Genome-wide Association Studies Identify Genetic Loci Associated with Albuminuria in Diabetes

Alexander Teumer[1,2]*, Adrienne Tin[3]*, Rossella Sorice[4]*, Mathias Gorski[5,6]*, Nan Cher Yeo[7]*, Audrey Y. Chu[8,9], Man Li[3], Yong Li[10], Vladan Mijatovic[11], Yi-An Ko[12], Daniel Taliun[13], Alessandro Luciani[14], Ming-Huei Chen[15,16], Qiong Yang[16], Meredith C. Foster[17], Matthias Olden[5,18], Linda T. Hiraki[19], Bamidele O. Tayo[20], Christian Fuchsberger[13], Aida Karina Dieffenbach[21,22], Alan R. Shuldiner[23], Albert V. Smith[24,25], Allison M. Zappa[26], Antonio Lupo[27], Barbara Kollerits[28], Belen Ponte[29], Bénédicte Stengel[30,31], Bernhard K. Krämer[32], Bernhard Paulweber[33], Braxton D. Mitchell[23], Caroline Hayward[34], Catherine Helmer[35], Christa Meisinger[36], Christian Gieger[37], Christian M. Shaffer[38], Christian Müller[39,40], Claudia Langenberg[41], Daniel Ackermann[42], David Siscovick[43], DCCT/EDIC[44], Eric Boerwinkle[45], Florian Kronenberg[28], Georg B. Ehret[46], Georg Homuth[47], Gerard Waeber[48], Gerjan Navis[49], Giovanni Gambaro[50], Giovanni Malerba[11], Gudny Eiriksdottir[24], Guo Li[43], H. Erich Wichmann[51-53], Harald Grallert[36,54,55], Henri Wallaschofski[56], Henry Völzke[1,2], Herrmann Brenner[57], Holly Kramer[20], I. Mateo Leach[58], Igor Rudan[59], J.L. Hillege[60], Jacques S. Beckmann[61,62], Jean Charles Lambert[63], Jian'an Luan[41], Jing Hua Zhao[41], John Chalmers[64], Josef Coresh[3,65], Joshua C. Denny[66], Katja Butterbach[57], Lenore J. Launer[67], Luigi Ferrucci[68], Lyudmyla Kedenko[33], Margot Haun[28], Marie Metzger[30,31], Mark Woodward[3,64,69], Matthew J. Hoffman[7], Matthias Nauck[2,56], Melanie Waldenberger[36], Menno Pruijm[70], Murielle Bochud[71], Myriam Rheinberger[72], N. Verweij[58], Nicholas J. Wareham[41], Nicole Endlich[73], Nicole Soranzo[74,75], Ozren Polasek[76], P. van der Harst[60], Peter Paul Pramstaller[13], Peter Vollenweider[48], Philipp S. Wild[77-79], R.T. Gansevoort[60], Rainer Rettig[80], Reiner Biffar[81], Robert J. Carroll[66], Ronit Katz[82], Ruth J.F. Loos[41,83], Shih-Jen Hwang[9], Stefan Coassin[28], Sven Bergmann[84], Sylvia E. Rosas[85], Sylvia Stracke[86], Tamara B. Harris[67], Tanguy Corre[84], Tanja Zeller[39,40], Thomas Illig[36,87,88], Thor Aspelund[24,25], Toshiko Tanaka[68], Uwe Lendeckel[89], Uwe Völker[2,47], Vilmundur Gudnason[24,25], Vincent Chouraki[63], Wolfgang Koenig[90-92], Zoltan Kutalik[62,84,93], Jeffrey R. O'Connell[23], Afshin Parsa[23], Iris M. Heid[5,37], Andrew D. Paterson[19,94], Ian H. de Boer[82], Olivier Devuyst[14], Jozef Lazar[95], Karlhans Endlich[73], Katalin Susztak[12], Johanne Tremblay[96], Pavel Hamet[97], Howard J. Jacob[7]**, Carsten A. Böger[6]**, Caroline S. Fox[9,98]**, Cristian Pattaro[13]**, Anna Köttgen[3,10]**

*indicates joint contribution
**indicates joint oversight

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Correspondence:

Anna Köttgen, MD MPH

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Medical Center – University of Freiburg
Berliner Allee 29
79110 Freiburg
Germany
Tel: +49 (0)761 270-78050
Fax: +49 (0)761 270-78040
anna.koettgen@uniklinik-freiburg.de

Alexander Teumer, PhD
University Medicine Greifswald
Walther-Rathenau-Str. 48
17475 Greifswald
Germany
Tel: +49 (0)3834 86 19579
Fax: +49 (0)3834 86 66 84
ateumer@uni-greifswald.de

Caroline S. Fox, MD MPH
NHLBI's Framingham Heart Study
73 Mt Wayte Ave Suite #2
Framingham, MA 01702
USA
Tel: +1 508 935-3447
Fax: +1 508 872-2678
foxca@nhlbi.nih.gov

Cristian Pattaro, PhD
European Academy of Bolzano/Bozen (EURAC) Center for Biomedicine
Via Galvani 31
I-39100 Bolzano
Italy
Tel +39 0471 055 527
Fax +39 0471 055 599
cristian.pattaro@eurac.edu

Affiliations

1. Institute for Community Medicine, University Medicine Greifswald, Walther-Rathenau-Str. 48, 17475 Greifswald, Germany.
2. DZHK (German Center for Cardiovascular Research), partner site Greifswald, Greifswald, Germany.
3. Dept. of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St, Baltimore, MD 21205, USA.

4. Institute of Genetics and Biophysics, "Adriano-Buzzati Traverso"-CNR, Via P. Castellino 111, 80131 Napoli, Italy.
5. Department of Genetic Epidemiology, Institute of Epidemiology and Preventive Medicine, University of Regensburg, D-93053 Regensburg, Germany.
6. Department of Nephrology, University Hospital Regensburg, Regensburg, Germany.
7. Department of Physiology, Medical College of Wisconsin, Milwaukee, WI, USA.
8. Preventive Medicine, Brigham and Women's Hospital, Boston MA, 900 Commonwealth Avenue East, Boston, MA 02215, USA.
9. NHLBI's Framingham Heart Study and the Center for Population Studies, 73 Mt Wayte Ave Suite #2, Framingham, MA 01702, USA.
10. Renal Division, Medical Center - University of Freiburg, Berliner Allee 29, 79110 Freiburg, Germany.
11. Department of Life and Reproduction Sciences, University of Verona, Strada Le Grazie 8, 37134 Verona, Italy.
12. Renal, Electrolyte and Hypertension Division, University of Pennsylvania, USA.
13. Center for Biomedicine, European Academy of Bozen/Bolzano (EURAC)-affiliated to the University of Lübeck, Bolzano, Italy.
14. University of Zurich, Institute of Physiology-Mechanisms of Inherited Kidney Disorders Group, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland.
15. Department of Neurology, Boston University School of Medicine, 72 East Concord ST B603, Boston, MA 02118, USA.
16. Department of Biostatistics, Boston University School of Public Health, 715 Albany Street, Boston, MA 02118, USA.
17. Tufts Medical Center, 800 Washington St Box 391, Boston, MA 02111, USA.
18. Department of Epidemiology and Preventive Medicine, Regensburg University Medical Center-Franz-Josef-Strau·-Allee 11, 93042 Regensburg, Germany.
19. Genetics and Genome Biology Program, The Hospital for Sick Children Research Institute, Toronto, Canada.
20. Loyola University Chicago, 2160 South First Avenue, Bldg 105, Maywood, IL 60153, USA.
21. Division of Clinical Epidemiology and Aging Research-German Cancer Research Center (DKFZ), Heidelberg, Germany.
22. German Cancer Consortium (DKTK)-Heidelberg, German.
23. Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA.
24. Icelandic Heart Association, Holtasmari 1, Kopavogur, Iceland.
25. Faculty of Medicine, University of Iceland, Vatnsmyrarvegur 16, Reykjavik.
26. Human and Molecular Genetics Center, Medical College of Wisconsin, Milwaukee, WI, USA.
27. Renal Unit, Department of Medicine, University of Verona, Italy.
28. Medical University of Innsbruck, Division of Genetic Epidemiology, Schöpfstraße 41, 6020 Innsbruck, Austria.
29. Nephrology Division, Department of Specialties of Internal Medicine, Geneva University Hospitals, Switzerland.
30. Inserm U-1018, CESP Team 5, Villejuif, France.
31. UMRS 1018, CESP Team 5, Univ Paris Sud, Univ Versailles St Quentin, France.

32. University Medical Centre Mannheim, 5th Department of Medicine, University of Heidelberg, Theodor Kutzer Ufer 1-3, 68167 Mannheim, Germany.
33. First Department of Internal Medicine, Paracelsus Medical University/ Salzburger Landeskliniken, Muellner Hauptstrasse 48, 5020 Salzburg, Austria.
34. MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, EH4 2XU Scotland, UK.
35. INSERM, U897; Bordeaux University; ISPED, Bordeaux, France.
36. Institute of Epidemiology II, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany.
37. Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany.
38. Vanderbilt University School of Medicine, 2215 B Garland Avenue 1224, Nashville, TN 37232, USA.
39. University Heart Center Hamburg, Martinistr. 52, 20246 Hamburg, Germany.
40. German Center for Cardiovascular Research (DZHK e.V.), partner site Hamburg, Lübeck, Kiel, 20246, Germany.
41. MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Box 285 Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK.
42. University Clinic for Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital and University of Bern, Switzerland.
43. Cardiovascular Health Research Unit, Departments of Epidemiology and Medicine, University of Washington, 1730 Minor Ave, Seattle, WA 98101, USA.
44. DCCT/EDIC Research Group.
45. Human Genetics Center, University of Texas Health Science Center, 1200 Herman Pressler Drive, Houston, TX 77030, USA.
46. Cardiology, Department of Specialties of Internal Medicine, Geneva University Hospitals, Geneva, Switzerland.
47. Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Friedrich-Ludwig-Jahn-Str. 15a, 17475 Greifswald, Germany.
48. Department of Internal Medicine, Lausanne University Hospital, Rue du Bugnon 46, CH-1011 Lausanne, Switzerland.
49. Department of Internal Medicine, University Medical Center Groningen-University of Groningen, The Netherlands.
50. Division of Nephrology, Department of Internal Medicine and Medical Specialties, Columbus-Gemelli University Hospital, Catholic University, Rome, Italy.
51. Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany.
52. Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany-Ingolstädter Landstr. 1, 85764 Neuherberg, Germany.
53. Institute of Medical Statistics and Epidemiology, Technical University Munich, Germany.
54. Research Unit of Molecular Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany.
55. German Center for Diabetes Research (DZD), Neuherberg, Germany.

56. Institute of Clinical Chemistry and Laboratory Medicine-University Medicine Greifswald, Ferdinand-Sauerbruch-Str., 17475 Greifswald, Germany.
57. Division of Clinical Epidemiology and Aging Research-German Cancer Research Center (DKFZ), Heidelberg, Germany.
58. University Medical Center Groningen, University of Groningen, Department of Cardiology-P.O. Box 30.001, 9700 RB Groningen, The Netherlands.
59. Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, Scotland, UK.
60. University Medical Center Groningen, University of Groningen, Department of Internal Medicine - Nefrology, P.O. Box 30001, 9700 RB Groningen, The Netherlands.
61. Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois and University of Lausanne-Rue du Bugnon 27, DGM 328, CH-1005 Lausanne, Switzerland.
62. Swiss Institute of Bioinformatics-Lausanne, Switzerland.
63. Inserm UMR 1167 " Risk factors and molecular determinants of aging-related diseases ", Institut Pasteur de Lille, 1 rue du Pr, Calmette 59019 Lille cedex, France.
64. The George Institute for Global Health, the University of Sydney, King George V Building, 83-117 Missenden Rd, Camperdown NSW 2050 Australia.
65. Welch Center for Prevention, Epidemiology and Clinical Research, 2024 E Monument St, Suite 2-600, Baltimore, MD 21287, USA.
66. Vanderbilt University School of Medicine, 448 Eskind Biomedical Library, 2209 Garland Ave. Nashville, TN 37212, USA.
67. Laboratory of Epidemiology and Population Sciences, Intramural Research Program, National Institute of Aging, National Institutes of Health, Bethesda, Maryland, USA.
68. Clinical Research Branch, National Institute on Aging-Baltimore MD 21250, USA.
69. The George Institute for Global Health, Nuffield Department of Population Health, University of Oxford, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK.
70. Service of Nephrology, Lausanne University Hospital, Rue du Bugnon 17, 1005 Lausanne, Switzerland.
71. University Institute of Social and Preventive Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne-Route de la Corniche 2, CH-1066 Epalinges, Switzerland.
72. Department of Nephrology, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, D-93053 Regensburg, Germany.
73. Institute of Anatomy and Cell Biology, University Medicine Greifswald, Friedrich-Loeffler-Str. 23c, 17475 Greifswald, Germany.
74. Human Genetics, Wellcome Trust Sanger Institute, Genome Campus, Hinxton, CB10 1HH, UK.
75. Department of Haematology, University of Cambridge, Hills Rd, Cambridge CB2 0AH, UK.
76. Croatian Centre for Global Health, Faculty of Medicine, University of Split, Croatia.
77. Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg-University Mainz, Germany.
78. Preventive Cardiology and Preventive Medicine, Dept. of Medicine 2, University Medical Center of the Johannes Gutenberg-University Mainz, Germany.
79. DZHK (German Center for Cardiovascular Research), Partner Site RhineMain, Mainz, Germany.
80. Institute of Physiology, University Medicine Greifswald, 17475 Greifswald, Germany.

81. Clinic for Prosthetic Dentistry, Gerostomatology and Material Science, University Medicine Greifswald, 17475 Greifswald, Germany.
82. Kidney Research Institute, Department of Medicine, University of Washington, 325 9th Ave, Seattle, WA 98104, USA.
83. Genetics of Obesity and Related Metabolic Traits Program, The Charles Bronfman Institute for Personalized Medicine, The Mindich Child Health and Development Institute, The Icahn School of Medicine at Mount Sinai, New York, USA.
84. Department of Medical Genetics, University of Lausanne-Rue du Bugnon 27, CH-1005 Lausanne, Switzerland.
85. Kidney and Hypertension Section, Joslin Diabetes Center and Harvard Medical School, Boston, MA, USA.
86. Clinic for Internal Medicine A, University Medicine Greifswald, Ferdinand-Sauerbruch-Str., 17475 Greifswald, Germany.
87. Institute for Human Genetics, Hannover Medical School, Carl-Neuberg-Strasse 1, 30625 Hanover, Germany.
88. Hannover Unified Biobank, Hannover Medical School, Carl-Neuberg-Strasse 1, 30625 Hanover, Germany.
89. Institute of Medical Biochemistry and Molecular Biology, University Medicine Greifswald, Ferdinand-Sauerbruch-Str., 17475 Greifswald, Germany.
90. Abteilung Innere II, Universitätsklinikum Ulm, Albert-Einstein-Allee 23, 89081 Ulm, Germany.
91. Deutsches Herzzentrum München, Technische Universität München, Lazarettstr. 36, 80636 Munich, Germany.
92. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany.
93. University Institute of Social and Preventive Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Route de la Corniche 10, CH-1010 Lausanne, Switzerland.
94. Dalla Lana School of Public Health, University of Toronto, Canada.
95. Department of Dermatology, Medical College of Wisconsin, Milwaukee, WI, USA.
96. CRCHUM, University of Montreal, 2901, Rachel East- office 401, Montreal (Quebec) H1W 4A4, Canada.
97. CRCHUM, University of Montreal, CHUM Research Center, Technopìle Angus, Montreal, Canada.
98. Division of Endocrinology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

Abstract

Elevated concentrations of albumin in the urine, albuminuria, are a hallmark of diabetic kidney disease and associate with increased risk for end-stage renal disease and cardiovascular events. To gain insight into the pathophysiological mechanisms underlying albuminuria, we conducted meta-analyses of genome-wide association studies and independent replication in up to 5,825 individuals of European ancestry with diabetes mellitus and up to 46,061 without diabetes, followed by functional studies. Known associations of variants in *CUBN*, encoding cubilin, with the urinary albumin-to-creatinine ratio (UACR) were confirmed in the overall sample ($p=2.4*10^{-10}$). Gene-by-diabetes interactions were detected and confirmed for variants in *HS6ST1* and near *RAB38*/*CTSC*. SNPs at these loci demonstrated a genetic effect on UACR in individuals with but not without diabetes. The change in average UACR per minor allele was 21% for *HS6ST1* and 13% for *RAB38*/*CTSC* ($p=6.3*10^{-7}$ and $5.8*10^{-7}$, respectively). Experiments using streptozotocin-treated diabetic *Rab38* knockout and control rats showed higher urinary albumin concentrations and reduced amounts of megalin and cubilin at the proximal tubule cell surface in *Rab38* knockout vs. control rats. Relative expression of *RAB38* was higher in tubuli of patients with diabetic kidney disease compared to controls. The loci identified here confirm known and highlight novel pathways influencing albuminuria.

Introduction

Urinary albumin and serum creatinine are two biomarkers recommended for routine assessment of chronic kidney disease (CKD).(1) Even at physiological rates of glomerular filtration, small elevations in urinary albumin concentrations are associated with an increased risk for CKD progression, end-stage renal disease (ESRD), cardiovascular events and both cardiovascular and all-cause mortality.(2–4) Patients with diabetes mellitus are at particularly high-risk for CKD and its sequelae: the prevalence of CKD among individuals with diabetes is >40% compared to about 10% in the general U.S. adult population,(5) and the presence of CKD is an important contributor to the excess mortality in diabetes.(6) The appearance of significant amounts of albumin in the urine (albuminuria) is a hallmark of diabetic kidney disease (DKD), the incidence of which continues to rise along with type 2 diabetes worldwide.(7) Even in treated individuals, residual diabetes-related microvascular risk represents an important challenge,(8) and DKD remains the leading cause of ESRD. No new effective treatments for DKD have been approved in more than two decades,(9) highlighting the importance to better understand its underlying mechanisms.

Using genome-wide association study (GWAS) meta-analysis in general population cohorts, we previously identified a missense single nucleotide polymorphism (SNP) in the gene encoding cubilin (*CUBN*) in association with the urinary albumin-to-creatinine ratio (UACR).(10) *CUBN* is currently the only genome-wide significant locus for UACR. However, this variant explains only a small fraction of the previously reported heritability of albuminuria ranging from 0.2-0.46 in the general population and those with diabetes,(11–13) suggesting that additional genetic variants remain to be found. Here we report the results of a GWAS meta-analysis of albuminuria traits in the general population performed in almost twice the sample size of our

previous study,(10) with a special focus on those with diabetes, replication in additional independent individuals, and follow-up investigations in human tissues and a genetically modified animal model of diabetes mellitus.

Research Design and Methods

Study Populations

Our study was based on 30 discovery and replication studies mostly from the general population, with the exception of ADVANCE and GENDIAN that enrolled exclusively individuals with type 2 diabetes, totaling 67,452 participants of European ancestry across the different analyses (up to 7,787 with diabetes in discovery and replication). The study characteristics, including the distribution of albuminuria and diabetes, are shown in **Supplementary Table 1**. Study protocols were approved by each local Institutional Review Board or Ethics Committee, and all human participants gave written informed consent.

Phenotype Definitions and Analytical Strategy

The measurement of urinary albumin and creatinine in each study is reported in **Supplementary Table 2**. Urinary albumin values below the detection limit of the used assays were set to the lower limit of detection. Rather than using urinary albumin, the urinary albumin-to-creatinine ratio (UACR) was calculated as urinary albumin/urinary creatinine (mg/g) to account for differences in urine concentration. Microalbuminuria (MA) was defined as UACR >25 mg/g in women and >17 mg/g in men.(10) Diabetes was defined as fasting glucose ≥126 mg/dl, non-fasting glucose ≥200 mg/dl or treatment for diabetes, or – if this information was not available - based on self-report. Across studies, we evaluated two traits, UACR and MA, and performed

four GWAS meta-analyses: MA and UACR in the overall sample, as well as UACR – a continuous trait with higher statistical power - separately among those with and without diabetes. Diabetes-stratified genome-wide association analyses of MA were not performed due to limited sample size. Detailed information on each study's design, genotyping, imputation and data management is provided in **Supplementary Tables 2 and 3**.

Discovery Meta-Analysis, Replication and Power

Stringent quality control of the genetic data was performed at the individual study level and again at the meta-analysis level using state-of-the-art methods. Missing genotypes were imputed using the HapMap reference panels in 19 studies and the 1000 Genomes reference panels in two studies. Details of genotyping, imputation software, reference panels, and quality filters in each study are reported in **Supplementary Table 3**.

All studies performed GWAS following a standardized analysis protocol. In each study, the natural logarithm of UACR was taken. Subsequently, sex-specific residuals were obtained from linear regression models of ln(UACR) on age and study-specific covariates, including study center and genetic principal components to adjust for possible population stratification if applicable. The continuous sex-specific residuals were then combined and used as the dependent variable that was regressed on imputed allelic dosages for each SNP in the GWAS.

Prior to meta-analyses, all study-specific GWAS summary files underwent quality control using GWAtoolbox.(14) Genomic-control (GC)(15) correction was applied when the GC factor was >1. Inverse-variance weighted fixed-effects meta-analyses were then conducted using METAL.(16) The I^2 statistic was used to evaluate between-study heterogeneity.(17) All meta-analyses were carried out in duplicate by two independent researchers.

After meta-analysis, SNPs with average minor allele frequency (MAF) <0.01 were excluded, and another GC correction was applied. There were 2,191,945 SNPs with average MAF >0.05 and present in >50% of the studies, which were then clustered based on correlation (linkage disequilibrium pruning using $r^2 \leq 0.2$) with the respective index SNP (the SNP with the lowest p-value) within windows of ±1 MB to identify independent SNPs with suggestive association ($p<10^{-5}$) in one or more of the four analyses.

Replication testing was then carried out for signals that were either genome-wide significant ($p<5*10^{-8}$) in any analysis, or showed suggestive association among those with diabetes, motivated by the clinical importance of DKD and the stronger association of the known and validated *CUBN* variant on UACR among those with diabetes.(18) Replication was defined as a one-sided p-value <0.05 in the meta-analysis of independent replication studies. Of the nine studies that contributed to replication, five studies used imputed dosage, and four studies performed replication genotyping of the index SNPs. A meta-analysis of the replication results was performed. Subsequently, the double GC-corrected results from the discovery meta-analysis and the results of the nine replication studies were meta-analyzed to obtain the overall statistical significance. Unless stated otherwise, all reported p-values are two-sided.

Assuming that associated SNPs explain a respective 0.6% and 0.5% of the UACR variance in diabetes (Table 1), there was 95% and 91% power, respectively, to replicate the seven suggestive loci from the discovery stage in an additional 1,800 samples with a 1-sided p-value <0.05.

Additional Analyses to Characterize Novel Loci

Replicated SNPs were further evaluated even in the absence of genome-wide significance because, in addition to the significant replication p-value, the low heterogeneity across cohorts and the biological plausibility of the *RAB38* locus further increased confidence in the findings. The SNPs were evaluated in the DCCT/EDIC study for association with a primary clinical endpoint defined as time from DCCT baseline until time to persistent microalbuminuria or a secondary endpoint of time to incident albumin excretion rate >300 mg /24h or end-stage renal disease.(10) Time to outcome development or censoring was determined as the number of visit years from DCCT baseline up to and including the 12th year of EDIC follow-up. Subjects with persistent microalbuminuria at DCCT baseline and DCCT year 1 were excluded from analyses of that outcome.

Epigenomic map analyses were performed as described previously(19) using data from human kidney and kidney proximal tubule epithelial cells that can be accessed at Gene Expression Omnibus (GSE49637).

Genetic associations with additional renal function traits, estimated glomerular filtration rate (eGFR) and CKD, were evaluated based on results from GWAS meta-analysis of the corresponding traits within the CKDGen Consortium (personal communication).

Gene Expression Analyses in Human Tissues

Quantification of transcript abundance in micro-dissected fractions of human glomeruli and tubuli from surgical nephrectomies, living allograft donors and portions of diagnostic kidney biopsies(20) was carried out using RNA-seq. Tissue from different renal compartments was separated using micro-dissection, homogenized and stored at -80°C. Total RNA of human proximal tubule fractions (n=256) and glomerular cells (n=48) were isolated using RNeasy Mini

Kit (Qiagen) according to manufacturer's instructions. RNA quality was assessed with the Agilent Bioanalyzer 2100, and RNA preparations exhibiting RIN scores >7 were used for cDNA synthesis. (library preparation at DNA Sequencing Core at UT Southwestern Medical Center). In short, 1 ug total RNA was used to isolate poly A purified mRNA using the Illumina TruSeq RNA Preparation Kit. Single-end 100bp sequencing was carried out, and the annotated RNA counts (fastq) were calculated by Illumina's CASAVA 1.8.2. Reads were mapped to the reference genome (NCBI build 37, hg19) using Spliced Transcripts Alignment to a Reference (STAR). Reads per kilobase of transcript per million mapped (RPKM) for *HS6ST1* and *RAB38* were compared between glomerular and tubular fractions using a two-sided t-test.

Comparison of candidate gene expression between cases with biopsy-proven DKD and healthy controls was based on publicly available micro-array data from human micro-dissected glomeruli and tubuli (Gene Expression Omnibus (GSE 30122).(20) Raw data were analyzed using the R package 'Affy' Version 1.44.0, expression levels were normalized using Robust Multi-array Average (RMA). Transcript abundance between patients and controls was compared using two-sided t-tests; statistical significance was defined as $p<8.3*10^{-3}$ (alpha of 0.05 corrected for six comparisons).

Studies of Rab38 in Rats

To better understand the association of *RAB38* with albuminuria in diabetes, we studied genetically modified rat models of diabetes. Eight *Rab38* knockout (KO) rats on a Fawn-hooded hypertensive (FHH) background, seven rats transgenic for the wild-type Brown Norway rat *Rab38* allele, and seven congenic rats were generated and raised as described previously.(21–23) *Rab38* KO rats did not express the protein.(22) These references also describe the recording

of blood pressure and the measurement of glucose and albuminuria. Diabetes was induced by treating 9-week-old male rats with streptozotocin (STZ, Sigma-Aldrich, St. Louis, MO, 50mg/kg i.p.).

Paraffin blocks of rat kidney samples were sectioned (thickness 6µm) with a Leica RM2255 rotary microtome (Thermo-Fisher Scientific, Waltham, MA) on Superfrost Plus glass slides (12-550-15, Thermo-Fisher Scientific, Waltham, MA). Before staining, slides were deparaffinized in changes of CitriSolv (22-143-975, Thermo-Fisher Scientific, Waltham, MA) and 70% isopropanol. Antigen retrieval was accomplished by incubating in sodium citrate buffer (1.8% 0.1M citric acid, 8.2% 0.1M sodium citrate, in distillated water, pH 6.0) in a rice cooker for 30 minutes. Slides were blocked with PBS blocking buffer (1% BSA, 0.2% non-fat dry milk in PBS) for 30 minutes and stained with primary antibodies specific for megalin or cubilin diluted in blocking buffer overnight at 4°C. Sheep anti-megalin and rabbit anti-cubilin were kindly provided by Dr. P Verroust, INSERM, Paris, France. After two washes in 0.1% Tween 20 (v/v in PBS), slides were incubated with corresponding fluorophore-conjugated secondary antibodies (Invitrogen) diluted in blocking buffer at room temperature for 1 hour and counterstained with 10 µM Hoechst 33342 (Molecular Probes-Invitrogen, H1399). Slides were subsequently mounted in Prolong Gold Anti-fade reagent (Invitrogen), acquired on Leica SP5 confocal laser scanning microscope (Center for Microscopy and Image Analysis, University of Zurich) equipped with a Leica APO 63x NA 1.4 oil immersion objective.

All experiments were performed in compliance with National Institutes of Health Guide for Care and Use of Laboratory Animals, and all used protocols were approved by the local Institutional Animal Care and Use Committee.

Results

Discovery of Genomic Loci Associated with Albuminuria Traits

The discovery GWAS meta-analyses for the four traits included up to 20 studies and up to 54,450 individuals per trait. The median UACR in the 20 individual studies that contributed to the UACR meta-analysis ranged from 2.5 to 15.6 mg/g. Across all studies, the mean proportion of women was 53%, and the median of average age was 57 years. The prevalence of diabetes in the population-based studies ranged from 1 to 14% (**Supplementary Table 1**).

There was no evidence of systematic biases influencing the genome-wide association results as indicated by low genomic control parameters (**Supplementary Fig. 1**). Only SNPs in the previously identified *CUBN* locus showed genome-wide significant association with both UACR ($p=2.4*10^{-10}$, **Supplementary Table 4**, **Supplementary Fig. 2**) and MA ($p=1.3*10^{-10}$, **Supplementary Table 5, Supplementary Fig. 2**). The effect of the minor C allele of the index SNP rs10795433 on logarithmic UACR values was four-fold larger among 5,825 individuals with diabetes (0.19 log(mg/g), $p=2.0*10^{-5}$) compared to 46,061 individuals without diabetes (0.045 log(mg/g), $p=6.1*10^{-6}$, p-value for difference $6.2*10^{-3}$). This corresponds, for each additional C allele, to a 5% higher geometric mean of UACR (exp(0.045)) in non-diabetics compared to 21% higher average UACR in diabetics (exp(0.19)).

Suggestive associations were identified for all four analyses (**Supplementary Tables 4–7,** regional association plots in **Supplementary Fig. 3**). Among the clinically important group of individuals with diabetes, seven genomic loci contained one or more SNPs showing suggestive association with UACR. These were exclusively identified in the meta-analysis of individuals with diabetes and mapped into or near *HS6ST1*, *CNTN4*, *KBTBD8*, *TFAP2B*/*PKHD1*, *CHN2*, *WDR11*/*FGFR2*, and *RAB38*/*CTSC* (**Supplementary Table 7**). Following our analytical strategy, we

selected the index SNP in each of these seven regions for follow up among up to 1,962 independent individuals with diabetes.

The Supplementary PDF document contains the QQ and Manhattan plots of all GWAS meta-analyses, the regional association plots, tables with cohort descriptions and association results of SNPs at $p<10^{-5}$.

Replication Analyses Implicate RAB38/CTSC and HS6ST1 as Novel Loci for UACR in Diabetes

The replication analyses included 9 studies and up to 1,962 individuals with diabetes. The median UACR across replication studies ranged from 3.8 to 14.5 mg/g. The mean proportion of women was 49%, and the median of average age was 55 years. For the seven SNPs tested for replication (**Supplementary Table 8**), we assessed whether the one-sided p-value was <0.05 in the combined replication studies (see Methods). This was the case for two SNPs: intergenic rs649529 upstream of *RAB38*/downstream of *CTSC* on chromosome 11q14 (**Fig. 1a**) and the intronic variant rs13427836 in *HS6ST1* on chromosome 2q21 (**Fig. 1b**). As illustrated in **Fig. 1c**, each additional copy of the minor T allele of rs649529 at *RAB38*/*CTSC* was consistently associated with lower UACR among the 5,825 individuals in the discovery and 1,962 in the replication cohorts (combined $p=5.8*10^{-7}$, **Table 1**), with no evidence of heterogeneity across cohorts ($I^2=0\%$). This effect corresponded to 13% lower geometric mean of UACR per copy of the T allele. Similarly, rs13427836 in *HS6ST1* showed consistent effects across cohorts (combined $p=6.3*10^{-7}$, **Table 1**), with each copy of the T allele associated with approximately 21% higher mean UACR but moderate heterogeneity ($I^2=29.9\%$, **Fig. 1d**).

The association of both rs649529 near *RAB38*/*CTSC* and rs13427836 in *HS6ST1* was not found in individuals without diabetes (p=1.0 and p=0.76, respectively, **Table 2**). Differences in

the association with UACR among those with and without diabetes were significant (t-test for difference $p=6.9*10^{-6}$ for rs649529 and $p=1.7*10^{-5}$ for rs13427836). Effects for the index variant in *CUBN* are provided for comparison. We also evaluated the association of the replicated SNPs with MA in the setting of diabetes. Information was obtained from a subset of studies with sufficiently high numbers of individuals with diabetes and MA (n=2,552; ARIC, CHS, COLAUS, EPIC, FHS, KORAF3, KORAF4, and SHIP). Across cohorts, the odds ratio (OR) for MA for each copy of the minor allele was 0.84 for rs649529 near *RAB38* (p=0.019) and 1.39 for rs13427836 in *HS6ST1* ($p=7.8*10^{-4}$), consistent with the direction of the SNP effects on UACR.

Characterization of Genetic Effects by Markers of Kidney Function and Diabetes

Next we investigated whether the gene-by-environment interaction was also observed for the eGFR, another measure of kidney function, and/or diabetes or glycemic traits. There were no statistically significant associations between rs649529, rs13427836, rs10795433 and eGFR in those with diabetes or without diabetes (**Table 2**), nor any associations with CKD. There were also no statistically significant associations of these variants with type 2 diabetes, fasting blood glucose, or plasma hemoglobin A1c concentrations (**Table 2**), indicating that the observed associations pertain to albuminuria in the setting of diabetes rather than to diabetes or impaired glucose metabolism *per se*. A comprehensive search in the NHGRI GWAS Catalog(24) did not reveal any significant associations between the two validated SNPs or their proxies with other diseases or traits.

Variant Evaluation

Using publicly available data of genetic effects on gene expression,(25) we found an association

in *cis* between rs649529 and transcript levels of both *RAB38* ($p=5.4*10^{-6}$) and the neighboring *CTSC* ($p=7.6*10^{-7}$), consistent with a regulatory effect of this variant in whole blood. Corresponding data for kidney-specific tissues are currently not available, but we used epigenetic maps generated from human adult kidney tissue(19) (see Methods) to further examine the regulatory potential of index SNPs. The intronic index SNP in *HS6ST1* and several proxies mapped into enhancer regions. Similarly, the *CUBN* index variant rs10795433 mapped into an intronic enhancer region. The region in which the index variant at *RAB38*/*CTSC* is located was annotated as not mapped/repressed in these cells preventing further examination. All proxies in strong LD with these three index SNPs ($r^2>0.6$, 1000G v5 reference panel)(26) were intronic (*CUBN* and *HS6ST1*) or intergenic (*RAB38*/*CTSC*).

Clinical Characterization Including Gene Expression of Replicated Loci

In order to evaluate target tissues within the kidney, we characterized the identified loci using tissue-specific gene expression data. Clinical characterization was conducted using data from patients with DKD and healthy controls(27) and a prospective study of individuals with type 1 diabetes.(28)

We utilized publicly available data(27) to compare relative expression of *RAB38*, *CTSC* and *HS6ST1* between patients with biopsy-confirmed DKD and healthy controls (see Methods). After multiple testing correction, only *RAB38* expression levels were significantly different, with higher expression in tubuli of DKD patients compared to controls ($p=1.3*10^{-4}$, **Fig. 2a**). We also used RNA-seq data from micro-dissected human kidney samples to quantify *RAB38* and *HS6ST1* expression in human glomeruli and tubuli. *HS6ST1* showed higher expression levels than *RAB38*, and both genes showed higher expression in tubuli than in glomeruli (**Fig. 2b**). The difference

between tubular and glomerular expression was more pronounced for *RAB38* ($p=1.1*10^{-8}$) than for *HS6ST1* (p=0.015).

To investigate whether the effect of the replicated SNPs extended to kidney disease progression in the setting of type 1 diabetes, the SNPs were tested for association with incident MA (268 cases, primary endpoint) and a combined endpoint of time to macroalbuminuria or ESRD (133 cases, secondary endpoint) among up to 1,304 participants with type 1 diabetes in the DCCT/EDIC Study.(28) Neither SNP showed significant association (**Supplementary Table 9**).

Diabetic Rab38 Knock-out Rats Show Increased Urinary Albumin Excretion

We aimed to further substantiate our findings by obtaining experimental support. We focused on the examination of *RAB38* because it was the gene implicated by higher gene expression in tubuli of DKD patients compared to controls, and because previous studies of *Rab38* KO and transgenic rats have confirmed its role in albuminuria in FHH rats and highlighted a role in tubular albumin reuptake.(21,22) We thus examined these animals in the setting of diabetes as outlined in **Fig. 3a**. Injection of streptozotocin (STZ) in 9-week-old rats successfully induced diabetes in all strains (**Fig. 3b**). Blood glucose rose from normal values before injection of STZ (congenic 205±3 mg/dL, transgenic 227±11 mg/dL, KO 198±7 mg/dL) to high values that indicate severe hyperglycemia one week after STZ (congenic 422±35 mg/dL, transgenic 406±27 mg/dL, KO 420±21 mg/dL). At age 11, 12, and 13 weeks, blood glucose levels remained high and showed no significant differences between strains (**Fig. 3b**). There were no significant differences in mean arterial blood pressure between congenic, transgenic, and KO animals freely moving around the cage; all animal strains showed a tendency towards decreased blood pressure 3-4 weeks after injection of STZ (**Fig. 3c**).

As illustrated in **Fig. 3d**, *Rab38* KO animals showed a progressive increase in urinary albumin excretion that became statistically significant two weeks after injection of STZ. At 4 weeks post injection, *Rab38* KO animals had an albumin excretion of 79±14 mg/day, whereas albumin excretion was only 28±8 mg/day in transgenic ($p<0.01$) and 41±13 mg/day in congenic animals ($p<0.01$). These data indicate that diabetic rats without Rab38 are more susceptible to the development of albuminuria than congenic and transgenic animals with functional *Rab38* despite a similar degree of hyperglycemia in all animals. Kidney sections obtained from a subset of animals showed a higher average glomerulosclerosis score (2.9±0.3) compared to congenic (2.2±0.1) and transgenic (2.2±0.1) rats ($p<0.05$, **Supplementary Fig. 4**), but differences were subtler than the ones observed for urinary albumin excretion.

To further clarify how loss of *Rab38* may lead to albuminuria, we performed immunohistochemistry staining of megalin and cubilin, known to mediate albumin re-uptake in the proximal tubulus, in kidney sections of all three animal strains. There was a marked reduction of both cubilin and megalin at the luminal membrane of proximal tubular cells in *Rab38* KO rats compared to congenic and transgenic control animals (**Fig. 3e**), consistent with a role of Rab38 in regulating the abundance of cubilin and megalin at the cell surface. In contrast, there was no significant difference in the number of structures positive for the lysosomal marker LAMP1 among the three strains.

Discussion

In this GWAS discovery meta-analysis of 2,191,945 SNPs in up to 54,450 participants of 20 studies, we replicated the association of the previously identified *CUBN* locus and UACR as well as MA at genome-wide significance and identified several suggestive signals among individuals

with diabetes. Two of these loci, *RAB38/CTSC* and *HS6ST1*, showed evidence of independent replication and *RAB38* was further supported by functional studies in a rat model. Our findings point to mechanisms in renal handling of albumin that associate with albuminuria in humans in the setting of diabetes. They thus represent examples of gene-by-diabetes interactions resulting in a complex trait that manifests when both environmental exposure and genetic susceptibility variants occur together.(29)

Not all individuals with diabetes develop DKD, suggesting that neither the presence of hyperglycemia nor genetic variants alone are sufficient to elicit the renal damage that typically manifests itself as albuminuria in diabetes. Our observations therefore raise the question of how the diabetic environment may result in the manifestation of genetic effects on albuminuria. The lack of association between both genetic variants and type 2 diabetes or specific glycemic measures in humans indicates that their effects occur without influencing diabetes *per se.* This notion is further substantiated by the fact that diabetic *Rab38* KO rats showed higher urinary albumin concentrations compared to controls despite the presence of similar blood glucose concentrations.

A difference between our observations in humans and rats is that the effect of genetic variation near *RAB38* on albuminuria was only found in humans with but not without diabetes, whereas *Rab38* KO rats without diabetes also progress to albuminuria.(22) A potential explanation is that KO rats represent a null mutation, allowing for the genetic component to take full effect without needing further aggravation by environmental factors. Conversely, many human susceptibility variants of complex traits do not result in a complete loss of function but instead are of regulatory nature. The effect of such variants may become apparent only upon an

environmental challenge, such that genetically determined alterations in renal albumin handling could manifest themselves in the setting of hyperglycemia and/or diabetes due to a number of mechanisms that secondarily impact albumin reabsorption, including an increased load of filtered albumin due to hyperfiltration or impairment of the glomerular filter. Along these lines, our observation of significantly higher *RAB38* transcript abundance in tubuli of DKD patients than controls may indicate an adaption of the tubular machinery for albumin reabsorption in this setting. Moreover, genetics effects of the index SNP at the *CUBN* locus on albuminuria were four times as large in individuals with compared to those without diabetes, supporting alterations of tubular albumin handling in the setting of diabetes.

RAB38 encodes a member of the small Rab GTPase protein family that regulate intracellular vesicle trafficking between organelles and are important in exo-, endo- and transcytosis.(30) Expression of Rab38 at the mRNA and protein level was observed in proximal tubule cells of wild-type rats.(31) FHH rats, a natural *Rab38* null mutation, show increased urinary albumin excretion without changes in their glomerular permeability.(21) In these animals, the expression of a Brown Norway *Rab38* transgene led to phenotypic rescue, and knockdown of *Rab38* in a proximal tubule cell system significantly decreased albumin endocytosis.(22) Together, these observations support an important role for the small Rab GTPase RAB38 in the reabsorption of filtered albumin.

Impaired RAB38 function may lead to increased albumin excretion via different mechanisms: altered intracellular vesicle transport may affect albumin reabsorption or recycling of reabsorbed albumin back to the plasma membrane.(32) Alternatively, altered RAB38 function may affect the delivery of proteins required for albumin endocytosis such as cubilin or megalin, the mechanism underlying albuminuria in Dent's disease.(33) Our experimental data showing

reduced abundance of cubilin and megalin in *Rab38* KO but not control rats is consistent with the latter hypothesis. Finally, it is also conceivable that impaired RAB38 function may directly cause glomerular damage, in turn leading to increased concentrations of urinary albumin.

Although the combined evidence from *Rab38* KO rats along with the gene expression and GWAS data strongly implicate *RAB38* as the gene underlying albuminuria in humans, the intergenic index SNP mapped upstream of *RAB38* and downstream of *CTSC* and was found to associate with transcript levels of both genes in whole blood. We can therefore not exclude the possibility that *CTSC* may be the causal gene underlying the observed associations, or that it contributes to the phenotype in addition to *RAB38*. *CTSC* encodes for a lysosomal cysteine protease. Rare mutations in the gene cause autosomal-recessive Papillon-Lefevre syndrome. No renal abnormalities have been reported in affected patients,(34) *Ctsc* KO mice do not show kidney abnormalities,(35) and the gene has not been linked to albuminuria or kidney disease.

The other genomic locus associated with albuminuria in diabetes contains *HS6ST1*, encoding the enzyme heparan sulfate (HS) 6-O-sulfotransferase that catalyzes the 6-O-sulfation of HS and heparin.(36,37) HS are anionic side-chains of HS proteoglycans, which are components of basement membranes, extracellular matrix and cell surfaces. Several studies have reported that inactivation or removal of HS lead to proteinuria, and biopsies from diabetic patients revealed changes in HS sulfation patterns compared with controls.(38) Thus, a genetic variant altering the enzyme's activity or abundance may lead to altered albuminuria. The underlying mechanisms could be manifold, as HS have been reported to not only impact glomerular filtration but also affect growth factor signaling, composition and functions of the glomerular basement membrane, and functions at the endothelial surface layer(38) and the proximal tubule.(39)

Strengths of our study include its large sample size, specific examination of individuals with diabetes, and consistent effects across a variety of studies underscoring the relevance of our findings at the general population level. In addition, we performed careful characterization of a replicated finding through *in vivo* experiments in *RAB38* KO and control rats that cannot, however, elucidate the exact mechanism by which genetic variation at this locus influences albuminuria in humans. Limitations include the fact that the replicated SNPs did not achieve genome-wide significance necessitating future confirmation in even larger studies, and that we could not assess allele-specific gene expression in human kidney tissues. We focused on European Ancestry study participants and mostly on individuals with type 2 diabetes. Future studies should therefore examine these associations among individuals of additional ancestries and in well-powered studies of patients with type I diabetes. Although results were combined after study-specific analyses, biological variation in UACR and different urine collection and storage methods may have resulted in increased variation and thus reduced statistical power to reveal significant associations. Additional studies are required to determine the causal variants and the exact underlying molecular mechanism by which genetic variation at *RAB38*/*CTSC* and *HS6ST1* associates with albuminuria in humans. An elucidation of the underlying mechanisms and the contributions and differences of albuminuria of glomerular and tubular origin may improve our understanding of proteinuric kidney diseases in general, but may be especially relevant to DKD, the most common cause of end-stage renal disease.

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Additional Data Resources
Data on glycemic traits have been contributed by MAGIC investigators and have been downloaded from www.magicinvestigators.org

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Author Contributions

B.S., C.H., J.T., P.H., G.E., L.L., T.B.H., V.G., A.K., A.D.P., N.J.W., C.S.F., B.K.K., P.S.W., A.L., G.G., Ch.M., C.G., H.E.W., P.P.P., M.J.H., H.J.J., J.L., B.P., H.V., M.N., R.R., R.B., J.C.D. and R.J.C. designed this study.

C.H., M.W., P.H., G.E., L.J.L., T.B.H., V.G., A.S., B.D.M., E.B., J.C., A.K., L.F., T.T., D.S., R.K., G.W., J.S.B., P.V., S.B., T.C., M.B., I.R., C.Ha., O.P., J.H.Z., A.K.D., H.B., K.B., N.J.W., C.S.F., B.K.K., P.S.W., G.G., Ch.M., C.G., H.E.W., H.G., M.Wa., T.I., W.K., J.L.H., Pvd.H., R.T.G., H.K., I.Hd.B., P.P.P., C.P.,

G.N., M.J.H., J.L., B.K., B.P., F.K., L.K., S.C., H.V., R.R., U.V., N.E, U.L., B.Po., D.A., G.B.E. and M.P. were involved in the study management.

C.H., P.H., G.E., V.G., A.S., J.C., O.D., O.P., N.J.W., C.S.F., B.K.K., P.S.W., A.L., G.G., Ch.M., C.G., H.E.W., J.L.H., Pvd.H., R.T.G., P.P.P., B.P., L.K., H.W., H.V., M.N., S.S. and R.J.C. recruited the subjects.

J.T., P.H., A.V.S., T.A., Ad.T., Y.L., M.L., J.C., A.K., R.S., A.D.P., C.S.F., M.R., V.M., M.G., B.O.T., C.P., N.C.Y., M.J.H., J.L., B.P., F.K., L.K., S.C., A.T. and K.H.E. interpreted the results.

J.T., P.H., Ad.T., M.L., A.K., Y.K., K.S., M.G., I.M.H., C.A.B., C.P., N.C.Y., M.J.H., H.J.J., J.L., A.T. and K.H.E. drafted the manuscript.

M.M., A.V.S., T.A., J.O., A.P., Ad.T., Y.L., M.L., M.F., A.K., G.L., R.K., R.S., Z.K., C.Ha., L.H., A.D.P., Y.K., K.S., Ji.L., M.H.C., Q.Y., M.O., S.J.H., M.R., C.M., V.M., M.G., I.M.H., C.A.B., B.O.T., S.E.R., D.T., C.F., C.P., N.V., N.C.Y., M.J.H., B.K., A.T., K.H.E., C.M.S., R.J.C. and A.Y.C. developed statistical methods and performed the analyses.

A.S., B.D.M., E.B., C.Ha., O.P., C.L., R.J.F.L., M.R., T.Z., N.S., H.G., M.Wa., T.I., A.M.Z., M.H., S.C., G.H. and U.V. performed the genotyping.

J.O., Y.L., Y.K., K.S., Ji.L., C.M., V.M., G.M., M.G., I.M.H., C.A.B., Pvd.H., D.T., N.V. and C.M.S. conducted the bioinformatics analyses.

N.C.Y., A.L., A.M.Z., M.J.H., O.D., H.J.J. and J.L. did the animal work or provided functional data.
All authors critically reviewed the manuscript.

Conflict of Interest Statement

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Tables

Table 1: Replicated SNP associations with UACR in individuals with diabetes

	sample size	effect on log(UACR[mg/g])	s.e.	p-value	I^2 %
rs649529, *RAB38*					
discovery	5825	-0.15	0.03	9.3E-06	0
replication	1962	-0.12	0.05	0.02	0
combined	7787	-0.14	0.03	5.8E-07	0
rs13427836, *HS6ST1*					
discovery	5509	0.20	0.04	6.1E-06	10
replication	1890	0.16	0.07	0.03	58
combined	7399	0.19	0.04	6.3E-07	30

For both variants, the effect of each additional copy of the minor allele (T) on UACR was modeled in an additive fashion. I^2 is provided as a measure of heterogeneity across studies. Imputation quality ranged from 0.41 to 1.0 for rs649529 and from 0.44 to 1.0 for rs13427836. The variants were directly genotyped in four of the replication studies, with a call rate ranging from 0.98 to 1 for rs649529 and of 0.99 for rs13427836. s.e.: standard error. The estimated proportion of explained variance in UACR among those with diabetes is 0.6% for rs649529 and 0.5% for rs13427836, using the formula 2*MAF*(1-MAF)*effect^2/var(log[UACR]), based on the combined effect estimates from Table 1 and the phenotypic variance in the large population-based ARIC Study.

Table 2: Replicated SNP associations with additional kidney function and diabetes-related traits

rs649529, *RAB38/CTSC*					
trait	**n**	**effect (OR)**	**s.e.**	**p-value**	**p-difference***
UACR, diabetes; log(mg/g)	7787	-0.14	0.03	5.8E-07	6.9E-06
UACR, no diabetes; log(mg/g)	45094	-0.004	0.008	0.64	
eGFRcrea, diabetes; log(ml/min/1.73m^2)	11527	0.003	0.004	0.46	2.8E-01
eGFRcrea, no diabetes; log(ml/min/1.73m^2)	118427	-0.001	0.001	0.59	
CKD (eGFR<60 ml/min/1.73m^2)	118114	(1.01)	0.02	0.57	
Type 2 diabetes	63390	(1.02)	0.02	0.32	
Fasting Glucose; (mmol/l)	46186	0.003	0.006	0.65	
HbA1c; (%)	46368	0.004	0.004	0.31	
rs13427836, *HS6ST1*					
trait	**n**	**effect (OR)**	**s.e.**	**p-value**	**p-difference***
UACR, diabetes; log(mg/g)	7399	0.19	0.04	6.3E-07	1.7E-05
UACR, no diabetes; log(mg/g)	34830	0.010	0.012	0.38	
eGFRcrea, diabetes; log(ml/min/1.73m^2)	11092	0.008	0.006	0.13	1.3E-01
eGFRcrea, no diabetes; log(ml/min/1.73m^2)	114247	0.000	0.001	0.94	
CKD (eGFR<60 ml/min/1.73m^2)	113612	(0.97)	0.02	0.23	
Type 2 diabetes	63390	(1.00)	0.03	0.94	
Fasting Glucose; (mmol/l)	46186	-0.005	0.004	0.22	
HbA1c; (%)	46368	0.003	0.005	0.61	
rs10795433, ***CUBN*†**					
trait	**n**	**effect (OR)**	**s.e.**	**p-value**	**p-difference***
UACR, diabetes; log(mg/g)	5825	0.19	0.04	2.0E-05	8.2E-04
UACR, no diabetes; log(mg/g)	46061	0.045	0.01	8.7E-06	
eGFRcrea, diabetes; log(ml/min/1.73m^2)	11522	0.007	0.005	0.18	0.19
eGFRcrea, no diabetes; log(ml/min/1.73m^2)	118299	0.0007	0.001	0.61	
CKD (eGFR<60 ml/min/1.73m^2)	118121	(1.04)	0.02	0.08	
Type 2 diabetes	63390	(1.00)	0.03	0.88	
Fasting Glucose; (mmol/l)	46186	-0.003	0.005	0.52	
HbA1c; (%)	46368	-0.002	0.005	0.73	

Effects represent the change in trait associated with each additional copy of the minor allele for each of the SNPs. For continuous traits, units are provided; the effect for binary outcomes, shown in parentheses, represents an odds ratio (OR). Estimates refer to the discovery samples of the respective trait and to the published resources for the glycemic traits. Fasting glucose and HbA1c were evaluated among individuals free of diabetes. For the kidney traits, p-values and standard errors are corrected using genomic control. *P-value for difference from a two-sample t-test: $t = (effect_{DM} - effect_{nonDM}) / (s.e._{DM}^2 + s.e._{nonDM}^2)$ which, for large sample sizes is distributed as a Normal (0,1). The correlation between $effect_{DM}$ and $effect_{nonDM}$ is assumed to be 0. s.e.: standard error. †Effect estimates for *CUBN* are provided from the discovery stage.

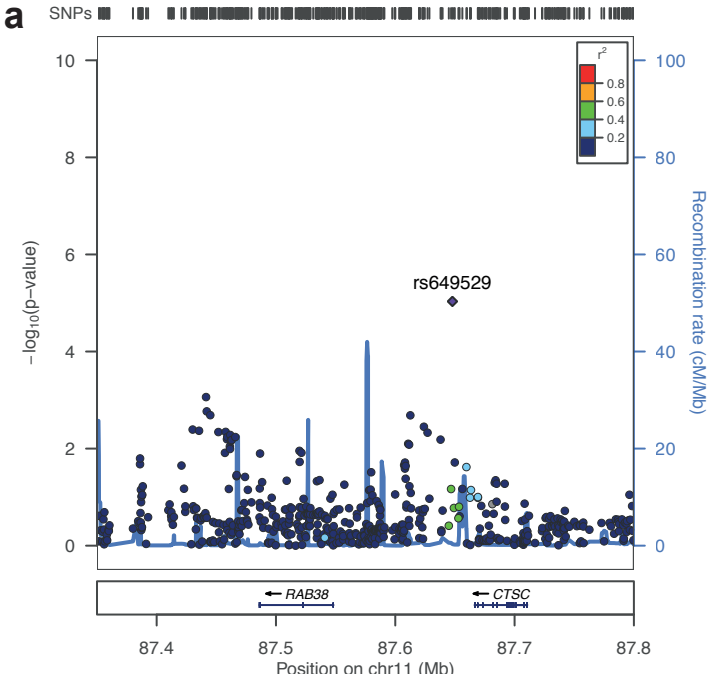
Associations with type 2 diabetes were tested using the publicly available summary statistics dataset from the DIAGRAM Consortium (12,171 cases and 56,862 controls).(40) Associations with fasting glucose and plasma hemoglobin A1c concentrations were evaluated using the publicly available results from the MAGIC Consortium (www.magicinvestigators.org).(41,42)

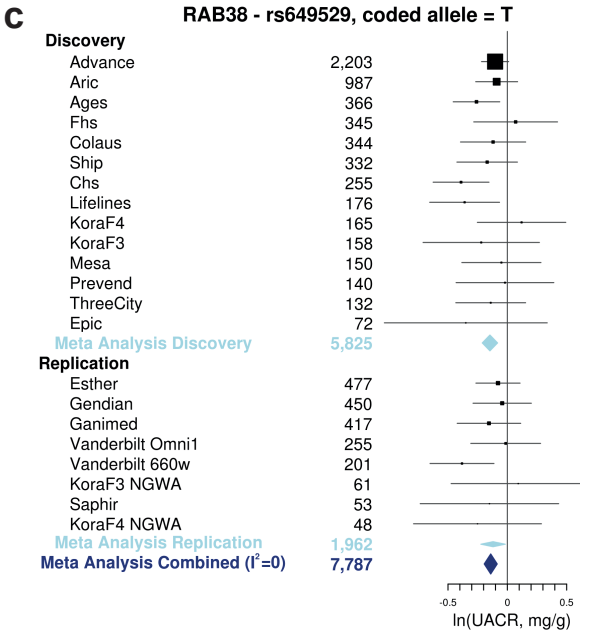
Figure Legends

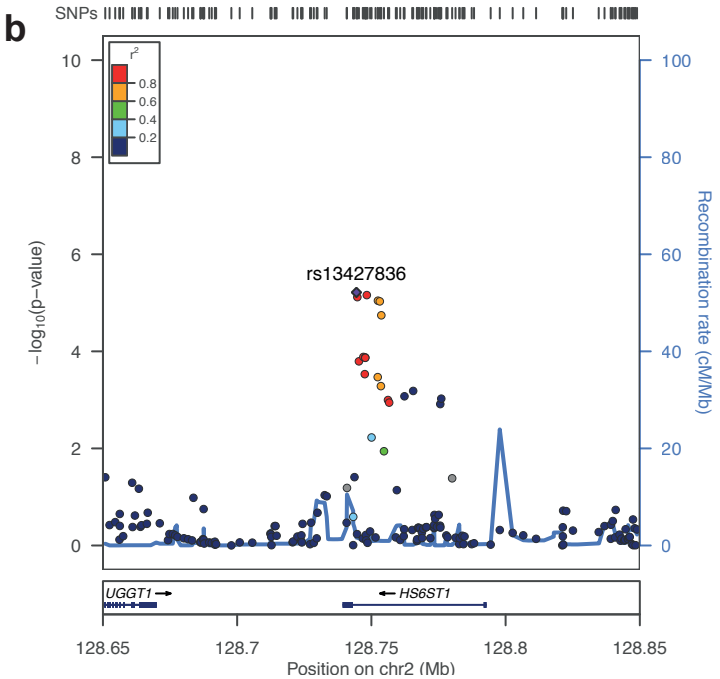
Figure 1: Overview of associated genomic loci at *RAB38*/*CTSC* and *HS6ST1* and consistent association with albuminuria in diabetes across the contributing studies. (a) Regional association plot of the *RAB38*/*CTSC* locus on chromosome 11 **(b)** The T allele at rs649529 is associated with lower UACR across discovery and replication studies **(c)** Regional association plot of the *HS6ST1* locus on chromosome 10 **(d)** The T allele of intronic rs13427836 is associated with higher UACR across discovery and replication studies.

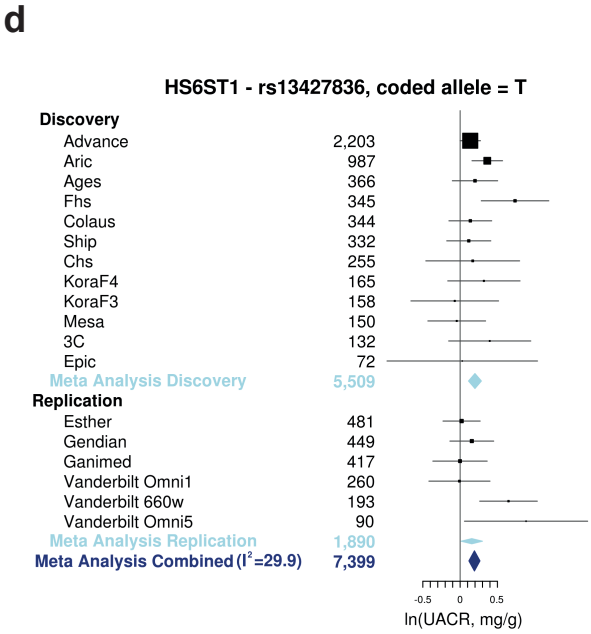
Figure 2: *RAB38* and *HS6ST1* expression across kidney tissues. (a) Comparison of *RAB38* and *HS6ST1* expression (microarray) in tubuli and glomeruli of patients with DKD and controls shows significantly higher *RAB38* expression in tubuli of DKD patients than in tubuli of controls (significance threshold $0.05/6=8.3*10^{-3}$ for investigating *RAB38*, *CTSC* and *HS6ST1* in tubuli and glomeruli)**.** *CTSC* expression was not significantly different between DKD cases and controls in tubuli (p=0.11) or glomeruli (p=0.03). Expression levels are shown as RMA-processed gene intensity values. Error bars correspond to the standard error of the mean (s.e.m.). **(b)** *RAB38* and *HS6ST1* transcript abundance quantified from RNA-seq is detected at high levels in human tubuli but also in glomerular cells. Transcripts were quantified by reads per kilobase of transcript per million mapped (RPKM). Error bars correspond to the standard error of the mean (s.e.m.).

Figure 3: Comparison of *Rab38* congenic, transgenic and KO rats after induction of diabetes. (a) Experimental setup and timeline **(b)** Comparison of blood glucose concentrations **(c)** Comparison of mean arterial pressure **(d)** Comparison of urinary albumin concentrations **(e)** Expression of endocytic markers. Immunofluorescence staining for megalin (green, top panel) and cubilin (red, bottom panel) in kidneys from all three rat strains. Nuclei counterstained with DAPI (blue). Scale bar, 50 µm. Data are presented as mean ± standard error of the mean (SEM). The results for blood pressure measurement, urinary albumin excretion, and blood glucose were analyzed by two-way ANOVA followed by Tukey's post hoc test.

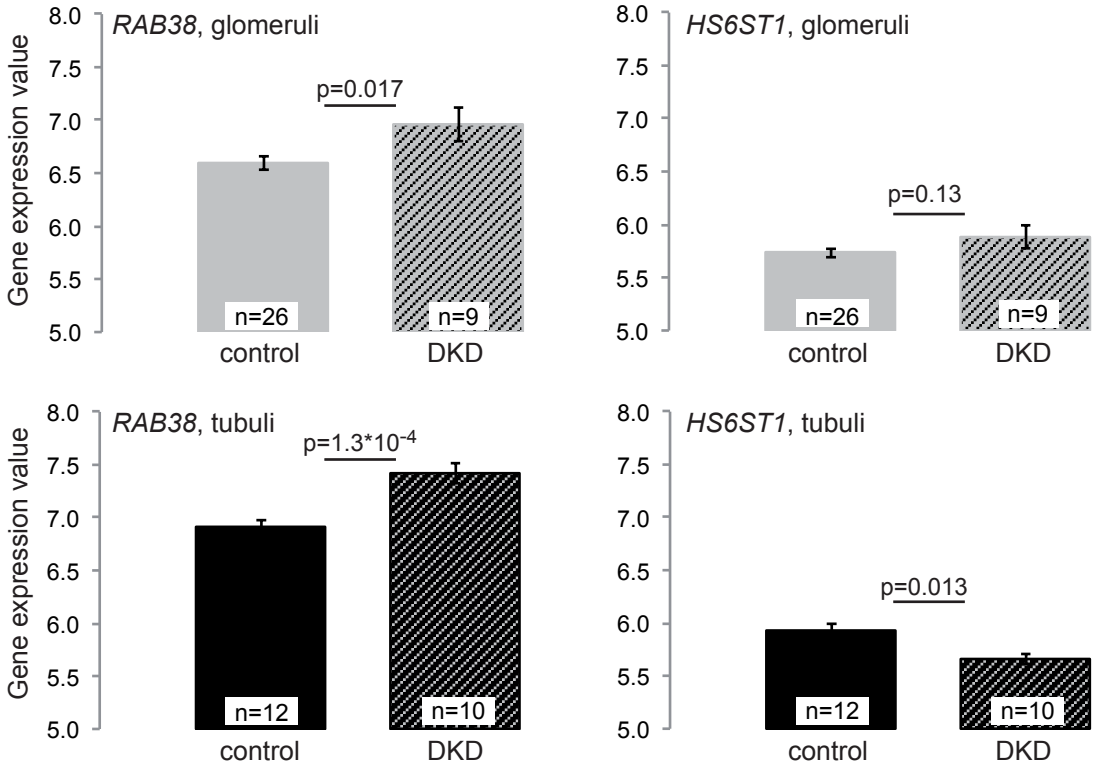

a
SNPs
rs649529
RAB38
CTSC
Position on chr11 (Mb)
Recombination rate (cM/Mb)


c
RAB38 - rs649529, coded allele = T
Discovery
Advance 2,203
Aric 987
Ages 366
Fhs 345
Colaus 344
Ship 332
Chs 255
Lifelines 176
KoraF4 165
KoraF3 158
Mesa 150
Prevend 140
ThreeCity 132
Epic 72
Meta Analysis Discovery 5,825
Replication
Esther 477
Gendian 450
Ganimed 417
Vanderbilt Omni1 255
Vanderbilt 660w 201
KoraF3 NGWA 61
Saphir 53
KoraF4 NGWA 48
Meta Analysis Replication 1,962
Meta Analysis Combined (I²=0) 7,787
ln(UACR, mg/g)

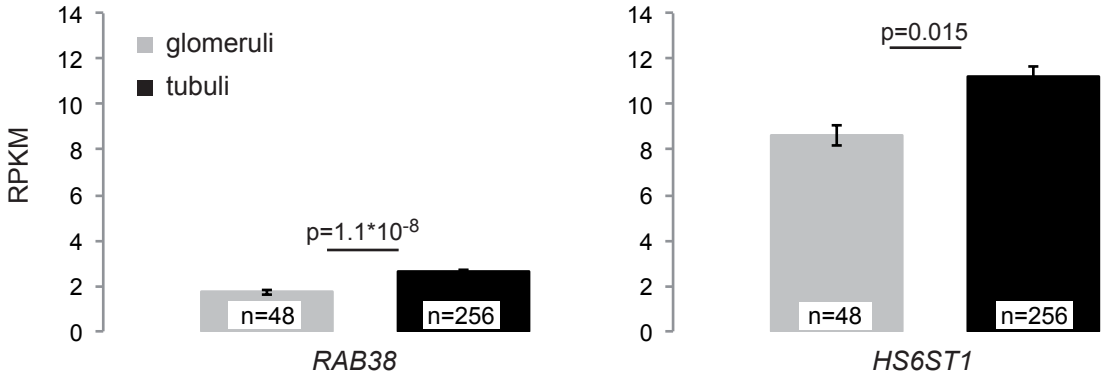

b
SNPs
rs13427836
UGGT1
HS6ST1
Position on chr2 (Mb)
Recombination rate (cM/Mb)

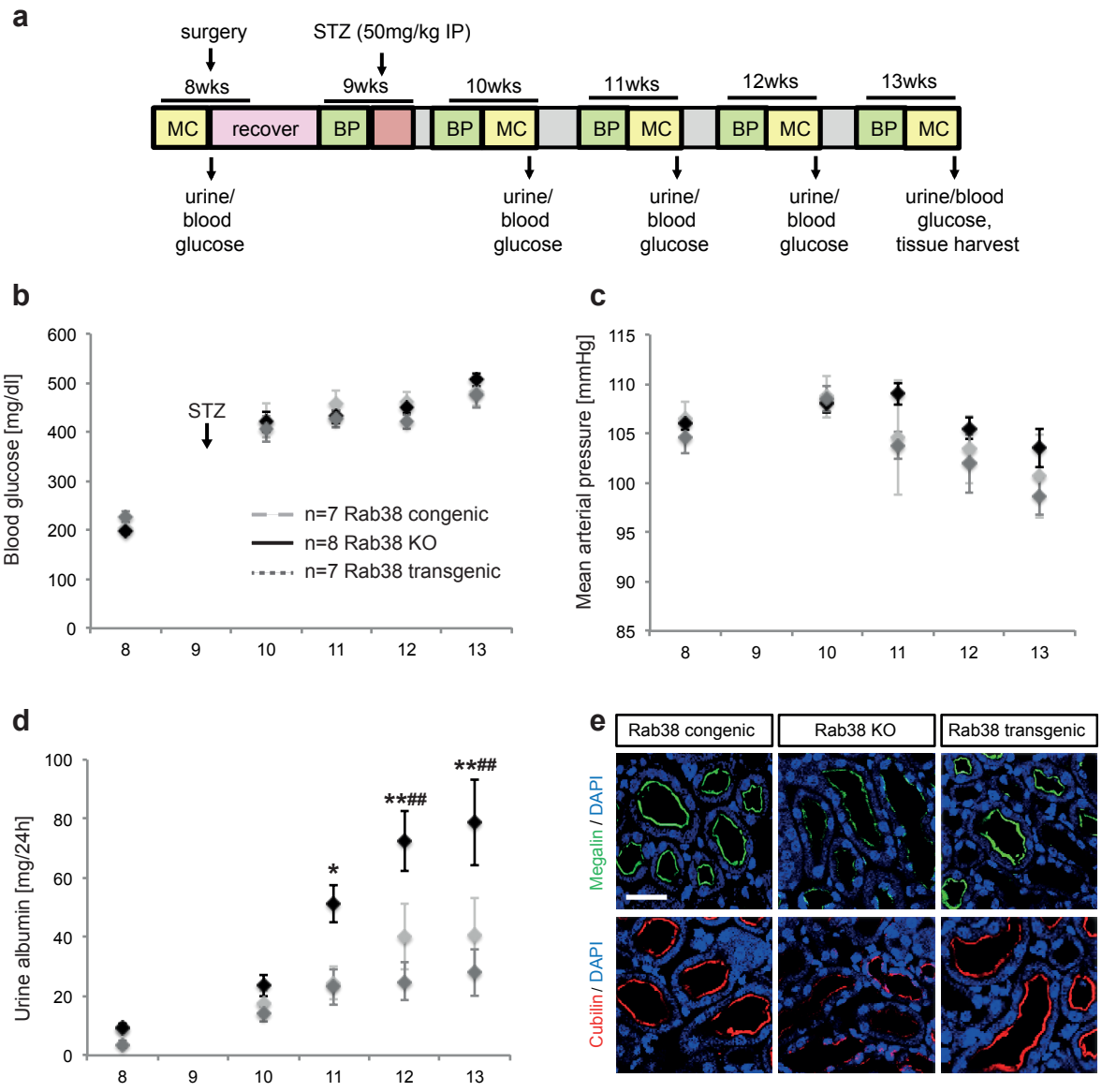

d
HS6ST1 - rs13427836, coded allele = T
Discovery
Advance 2,203
Aric 987
Ages 366
Fhs 345
Colaus 344
Ship 332
Chs 255
KoraF4 165
KoraF3 158
Mesa 150
3C 132
Epic 72
Meta Analysis Discovery 5,509
Replication
Esther 481
Gendian 449
Ganimed 417
Vanderbilt Omni1 260
Vanderbilt 660w 193
Vanderbilt Omni5 90
Meta Analysis Replication 1,890
Meta Analysis Combined (I²=29.9) 7,399
ln(UACR, mg/g)

a **Comparison of Relative Gene Expression, DKD Patients and Controls**



b **Comparison of Gene Expression (RNAseq) Across Tissues**




a
surgery
STZ (50mg/kg IP)
8wks
9wks
10wks
11wks
12wks
13wks
MC
recover
BP
urine/ blood glucose
urine/ blood glucose, tissue harvest
b
Blood glucose [mg/dl]
STZ
n=7 Rab38 congenic
n=8 Rab38 KO
n=7 Rab38 transgenic
c
Mean arterial pressure [mmHg]
d
Urine albumin [mg/24h]
*
**##
e
Rab38 congenic
Rab38 KO
Rab38 transgenic
Megalin / DAPI
Cubilin / DAPI

Genome-wide Association Studies Identify Genetic Loci Associated with Albuminuria in Diabetes

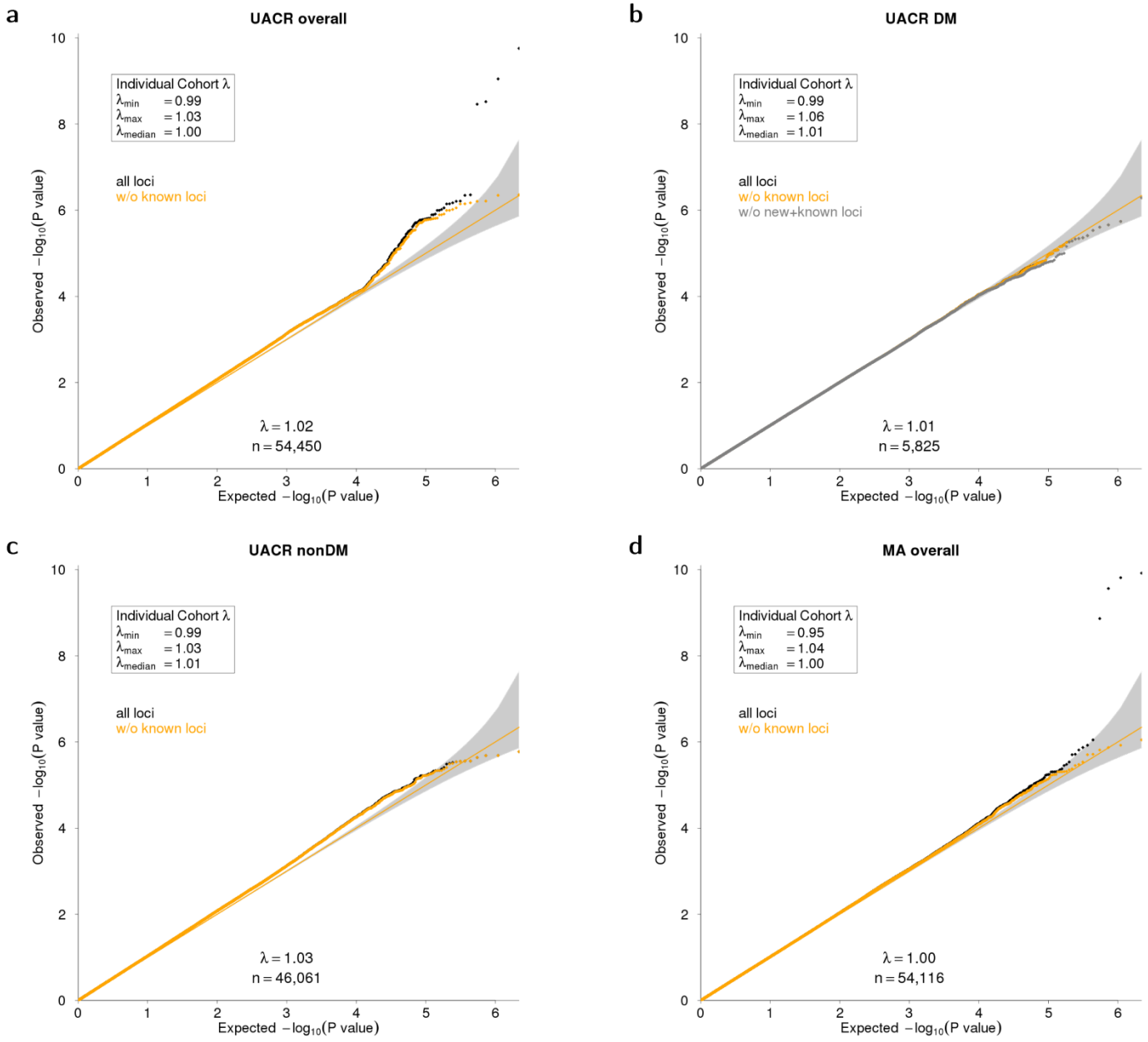
SUPPLEMENTAL MATERIALS

This work is dedicated to the memory of our colleague Dr. Wen Hong Linda Kao, a wonderful person, brilliant scientist and central member of the CKDGen Consortium.

Table of Contents

Supplementary Figure 1: QQ plots for all GWAS meta-analyses

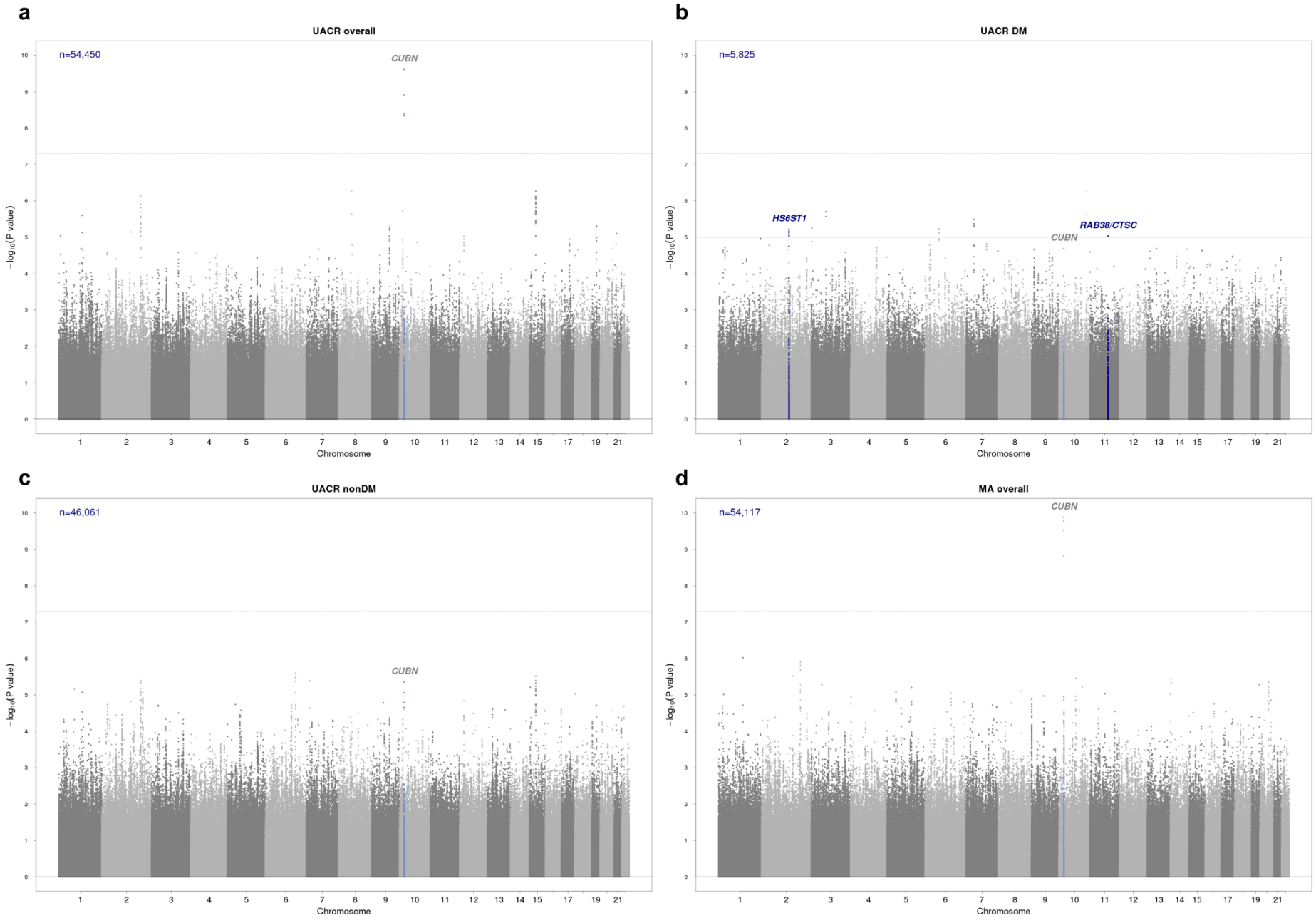
Quantile-quantile (QQ) plots of the GWAS meta-analysis results for (**a**) the urinary albumin-to-creatinine ratio (UACR) in the overall sample, (**b**) UACR among those with diabetes (**c**) UACR among those without diabetes, and (**d**) microalbuminuria (MA) in the overall sample. The observed p-values are plotted on the y-axis against their expected distribution under the null hypothesis of no association on the x-axis.



Results for all SNPs are shown in black, and results after removal of loci previously known to contain trait-associated variants are shown in yellow. Gray bands represent 95% confidence intervals. λ: lambda, genomic control parameter; n: sample size.

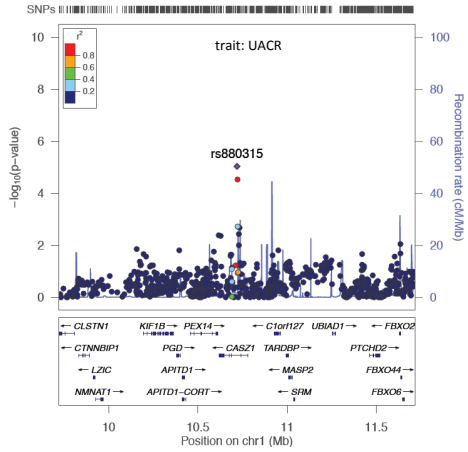
Supplementary Figure 2: Manhattan plots for all GWAS meta-analyses

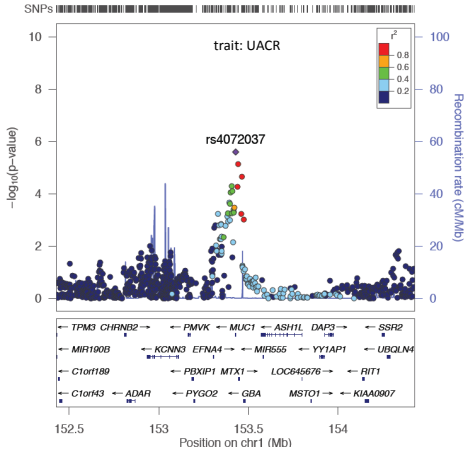
Manhattan plots of the GWAS meta-analysis results for (**a**) UACR in the overall sample, (**b**) UACR among those with diabetes, (**c**) UACR among those without diabetes, and (**d**) microalbuminuria in the overall sample. SNPs are plotted on the x-axis according to their position on each chromosome with the -log10(p-value) on the y-axis. The upper solid horizontal line indicates the threshold for genome-wide significance, $5*10^{-8}$. The lower solid horizontal line for UACR among those with diabetes (**b**) represents the threshold of $1*10^{-5}$ applied to select SNPs for replication. Genomic loci previously known to contain trait-associated variants are colored in light blue, new findings in dark blue.

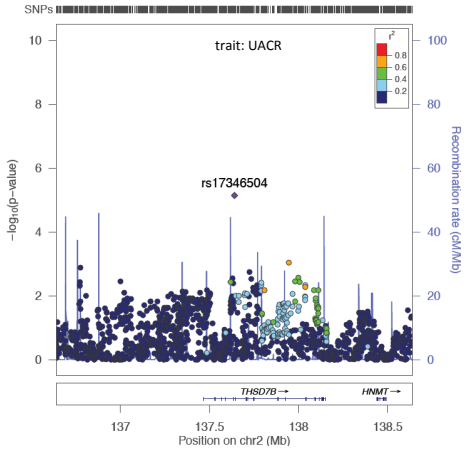

a
UACR overall
n=54,450
CUBN
b
UACR DM
n=5,825
HS6ST1
RAB38/CTSC
CUBN
c
UACR nonDM
n=46,061
CUBN
d
MA overall
n=54,117
CUBN
−log10(P value)
Chromosome
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 17 19 21

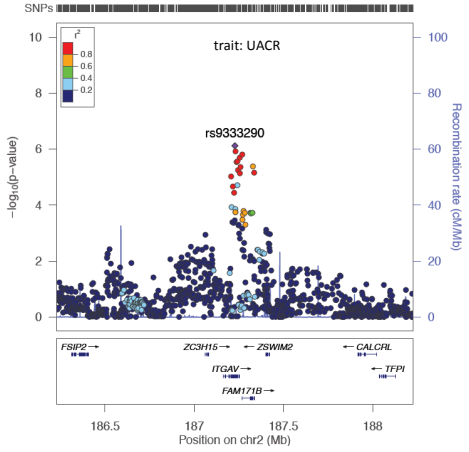
Supplementary Figure 3: Regional association plots

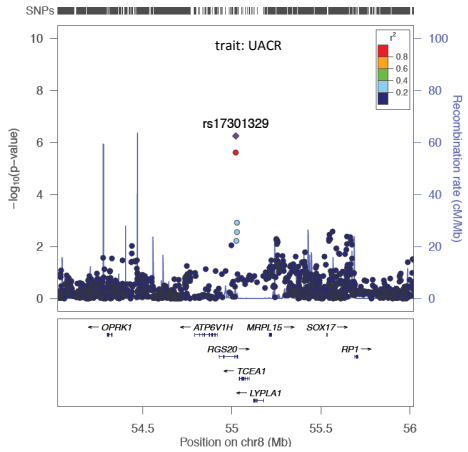
Regional association plots are shown for all loci that contained at least one index SNP associated with the trait at $p<10^{-5}$ after correction for genomic control. Correlation with the index SNP is estimated based on the HapMap r22 CEU samples. Plots were generated using the stand-alone version of LocusZoom (Pruim RJ *et al.*, Bioinformatics 2010). When association in a genomic region was observed with more than one trait, the regional association plot of the trait with the lowest p-value is shown. Genetic positions refer to NCBI build 36/hg18 coordinates.

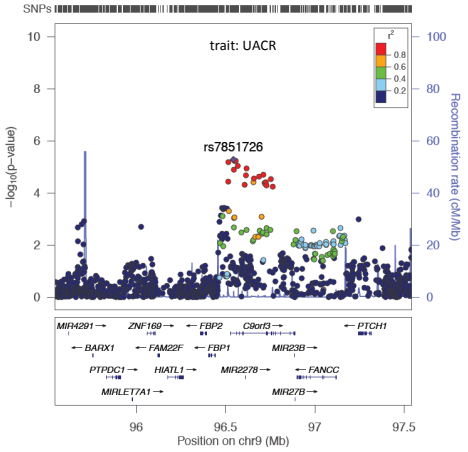

SNPs
trait: UACR
rs880315
−log10(p−value)
Recombination rate (cM/Mb)
CLSTN1
KIF1B
PEX14
C1orf127
UBIAD1
FBXO2
CTNNBIP1
PGD
CASZ1
TARDBP
PTCHD2
LZIC
APITD1
MASP2
FBXO44
NMNAT1
APITD1−CORT
SRM
FBXO6
Position on chr1 (Mb)

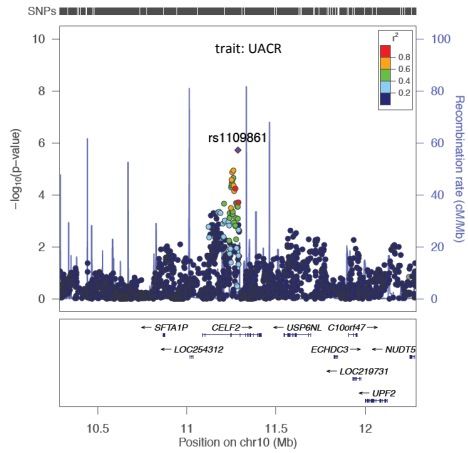

SNPs
trait: UACR
rs4072037
−log10(p−value)
Recombination rate (cM/Mb)
TPM3
CHRNB2
PMVK
MUC1
ASH1L
DAP3
SSR2
MIR190B
KCNN3
EFNA4
MIR555
YY1AP1
UBQLN4
C1orf189
PBXIP1
MTX1
LOC645676
RIT1
C1orf43
ADAR
PYGO2
GBA
MSTO1
KIAA0907
Position on chr1 (Mb)

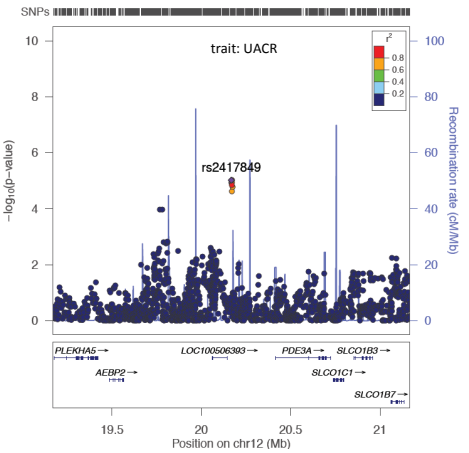

SNPs
trait: UACR
rs17346504
−log10(p−value)
Recombination rate (cM/Mb)
THSD7B
HNMT
Position on chr2 (Mb)

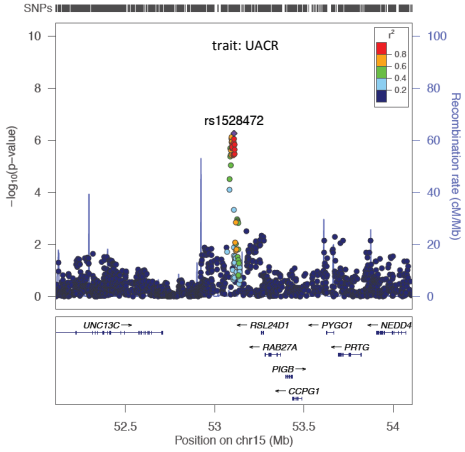

SNPs
trait: UACR
rs9333290
−log10(p−value)
Recombination rate (cM/Mb)
FSIP2
ZC3H15
ZSWIM2
CALCRL
ITGAV
TFPI
FAM171B
Position on chr2 (Mb)

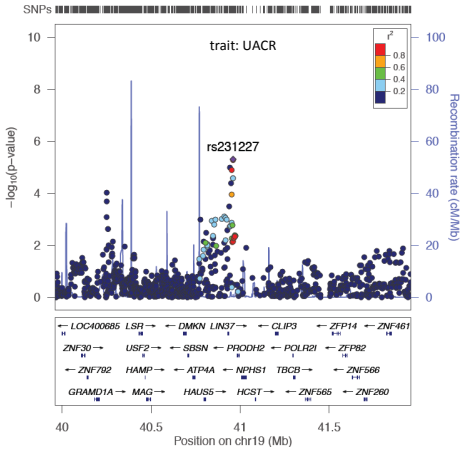

SNPs
trait: UACR
rs17301329
−log10(p−value)
Recombination rate (cM/Mb)
OPRK1
ATP6V1H
MRPL15
SOX17
RGS20
RP1
TCEA1
LYPLA1
Position on chr8 (Mb)

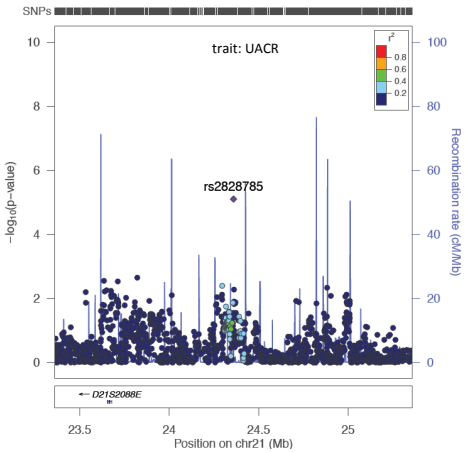

SNPs
trait: UACR
rs7851726
−log10(p−value)
Recombination rate (cM/Mb)
MIR4291
ZNF169
FBP2
C9orf3
PTCH1
BARX1
FAM22F
FBP1
MIR23B
PTPDC1
HIATL1
MIR2278
FANCC
MIRLET7A1
MIR27B
Position on chr9 (Mb)

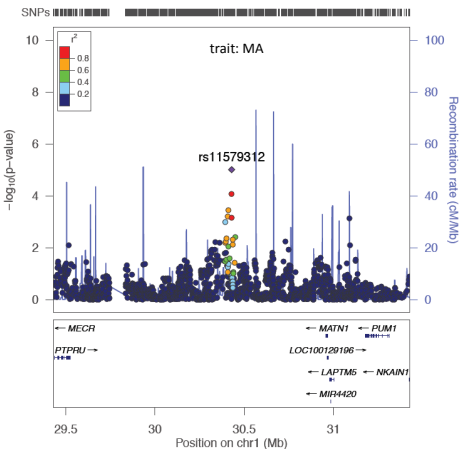

SNPs
trait: UACR
rs1109861
−log10(p−value)
Recombination rate (cM/Mb)
SFTA1P
CELF2
USP6NL
C10orf47
LOC254312
ECHDC3
NUDT5
LOC219731
UPF2
Position on chr10 (Mb)

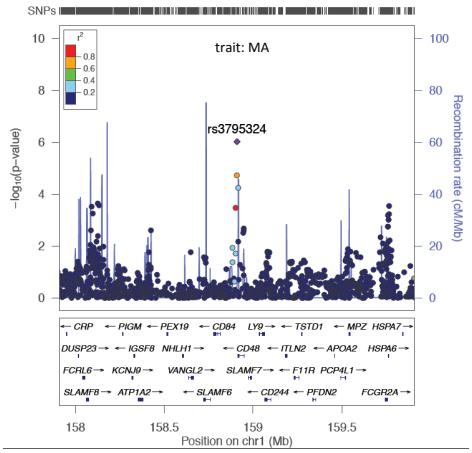

SNPs
trait: UACR
rs2417849
−log10(p−value)
Recombination rate (cM/Mb)
PLEKHA5
LOC100506393
PDE3A
SLCO1B3
AEBP2
SLCO1C1
SLCO1B7
Position on chr12 (Mb)


SNPs
trait: UACR
rs1528472
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
UNC13C
RSL24D1
PYGO1
NEDD4
RAB27A
PRTG
PIGB
CCPG1
52.5
53
53.5
54
Position on chr15 (Mb)


SNPs
trait: UACR
rs231227
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
LOC400885
LSR
DMKN
LIN37
CLIP3
ZFP14
ZNF461
ZNF30
USF2
SBSN
PRODH2
POLR2I
ZFP82
ZNF702
HAMP
ATP4A
NPHS1
TBCB
ZNF566
GRAMD1A
MAG
HAUS5
HCST
ZNF565
ZNF260
40
40.5
41
41.5
Position on chr19 (Mb)


SNPs
trait: UACR
rs2828785
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
D21S2088E
23.5
24
24.5
25
Position on chr21 (Mb)


SNPs
trait: MA
rs11579312
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
MECR
PTPRU
MATN1
PUM1
LOC100129196
LAPTM5
NKAIN1
MIR4420
29.5
30
30.5
31
Position on chr1 (Mb)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trait: MA
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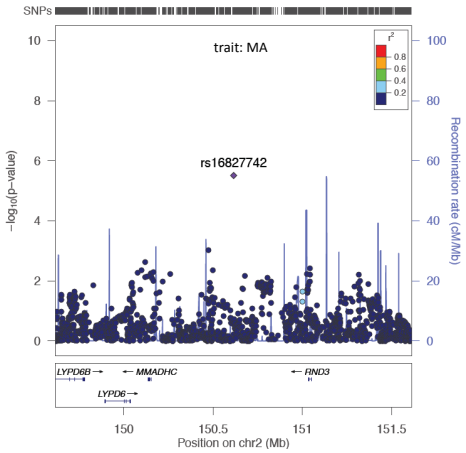
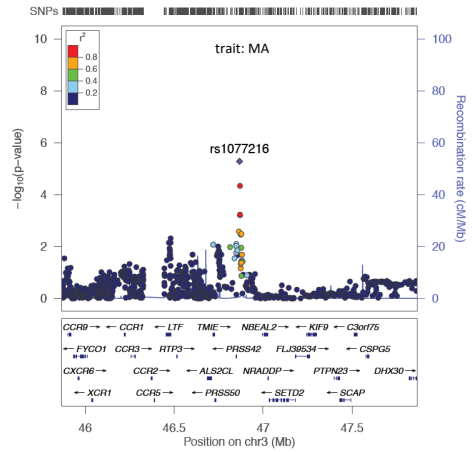
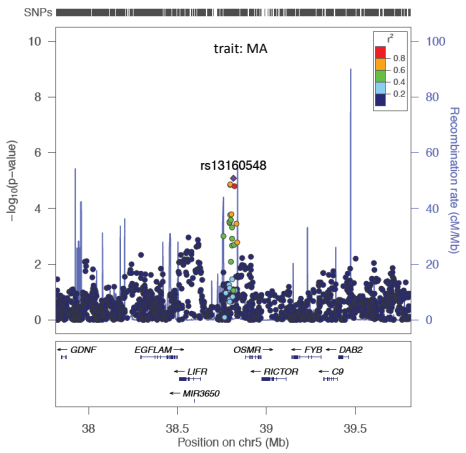
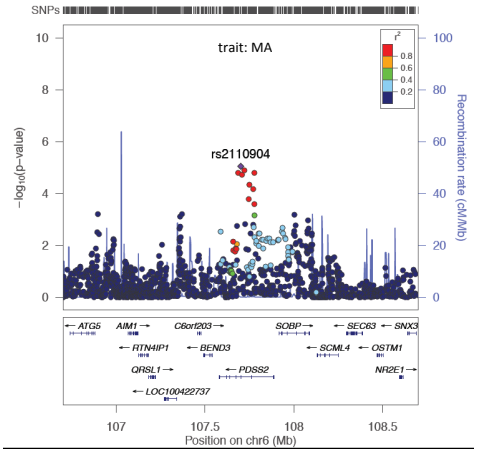
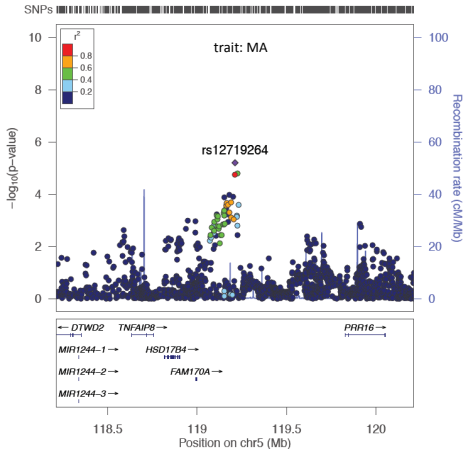
−log10(p-value)
Recombination rate (cM/Mb)
Position on chr1 (Mb)

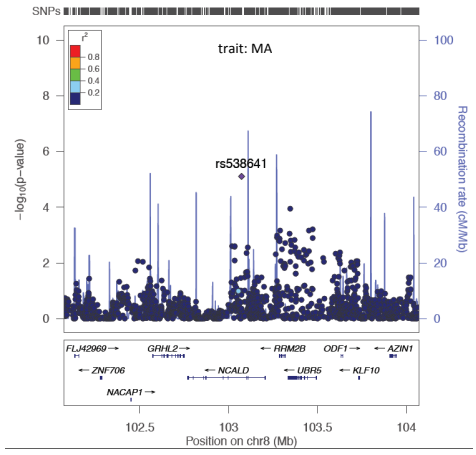

SNPs
trait: MA
rs16827742
−log10(p-value)
Recombination rate (cM/Mb)
Position on chr2 (Mb)

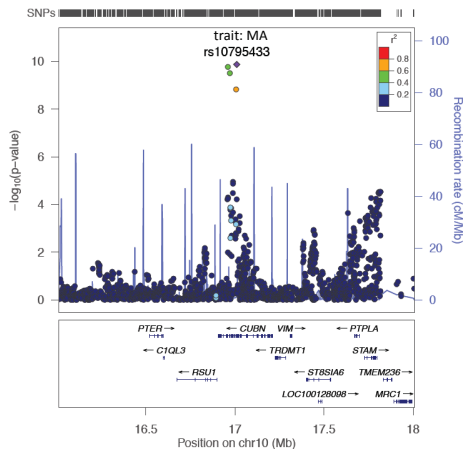

SNPs
trait: MA
rs1077216
−log10(p-value)
Recombination rate (cM/Mb)
Position on chr3 (Mb)

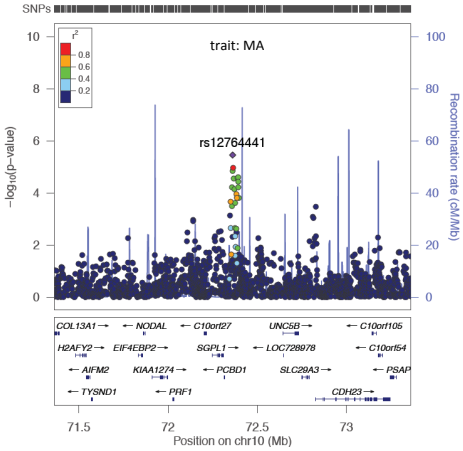

SNPs
trait: MA
rs13160548
−log10(p-value)
Recombination rate (cM/Mb)
Position on chr5 (Mb)

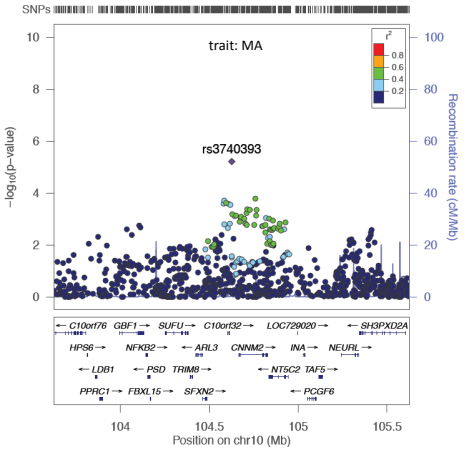

SNPs
trait: MA
rs2110904
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
ATG5
AIM1
C6orf203
SOBP
SEC63
SNX3
RTN4IP1
BEND3
SCML4
OSTM1
QRSL1
PDSS2
NR2E1
LOC100422737
107
107.5
108
108.5
Position on chr6 (Mb)

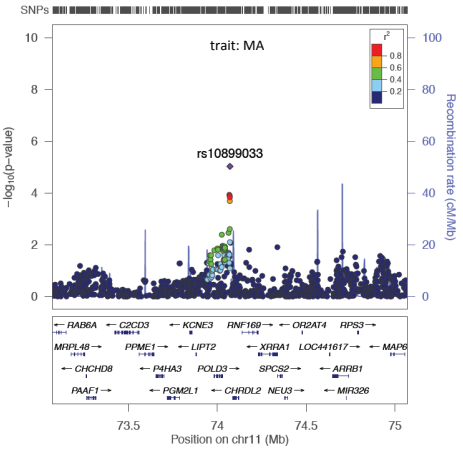

SNPs
trait: MA
rs12719264
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
DTWD2
TNFAIP8
PRR16
MIR1244-1
HSD17B4
MIR1244-2
FAM170A
MIR1244-3
118.5
119
119.5
120
Position on chr5 (Mb)

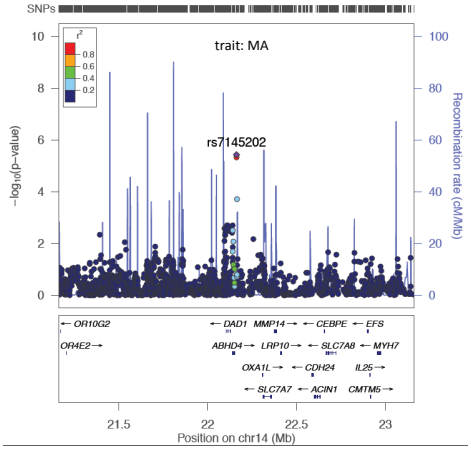

SNPs
trait: MA
rs538641
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
FLJ42969
GRHL2
RRM2B
ODF1
AZIN1
ZNF706
NCALD
UBR5
KLF10
NACAP1
102.5
103
103.5
104
Position on chr8 (Mb)

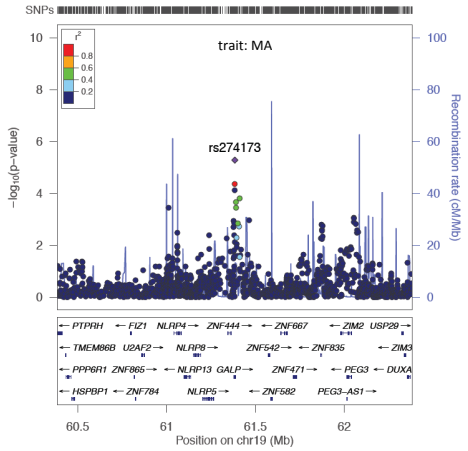

SNPs
trait: MA
rs10795433
r²
0.8
0.6
0.4
0.2
−log10(p-value)
Recombination rate (cM/Mb)
PTER
CUBN
VIM
PTPLA
C1QL3
TRDMT1
STAM
RSU1
STBSIA6
TMEM236
LOC100128098
MRC1
16.5
17
17.5
18
Position on chr10 (Mb)

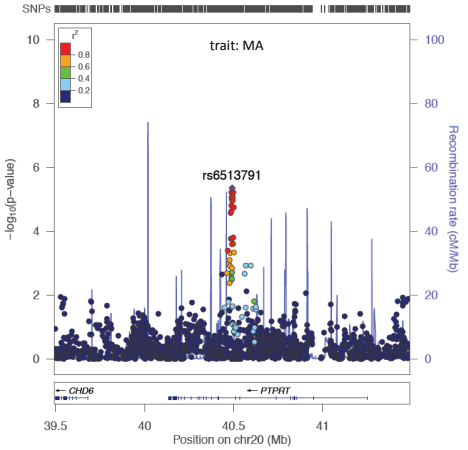

SNPs
trait: MA
rs12764441
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr10 (Mb)

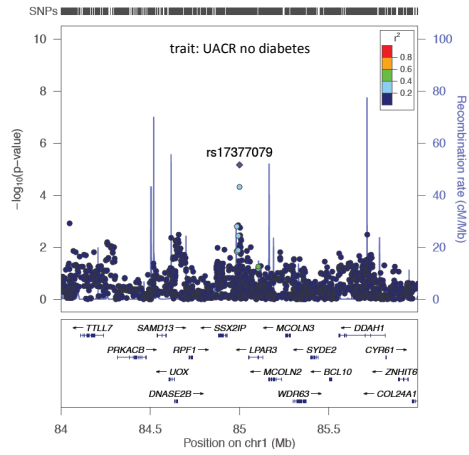

SNPs
trait: MA
rs3740393
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr10 (Mb)

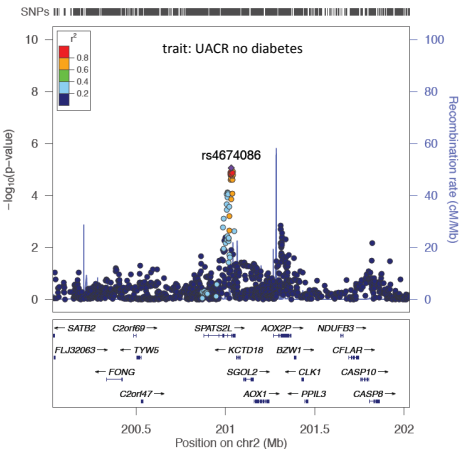

SNPs
trait: MA
rs10899033
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr11 (Mb)

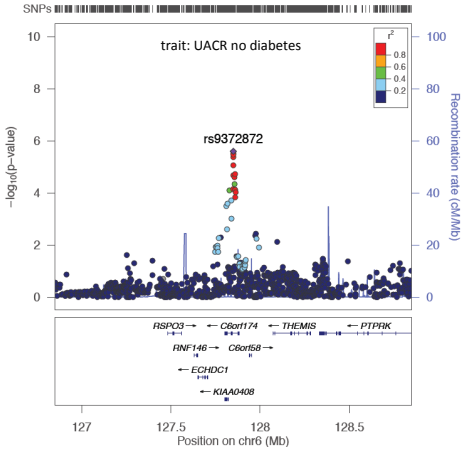

SNPs
trait: MA
rs7145202
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr14 (Mb)

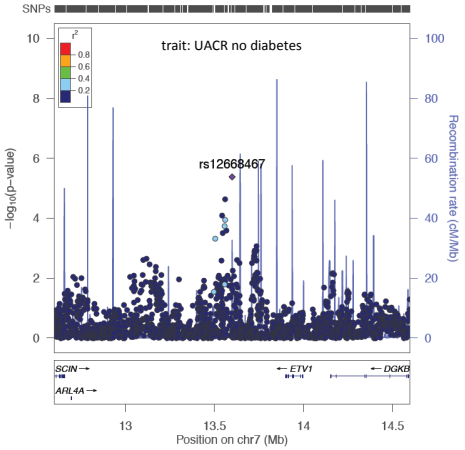

SNPs
trait: MA
rs274173
−log10(p−value)
Recombination rate (cM/Mb)
PTPRH FIZ1 NLRP4 ZNF444 ZNF667 ZIM2 USP29
TMEM86B U2AF2 NLRP8 ZNF542 ZNF835 ZIM3
PPP6R1 ZNF865 NLRP13 GALP ZNF471 PEG3 DUXA
HSPBP1 ZNF784 NLRP5 ZNF582 PEG3-AS1
Position on chr19 (Mb)

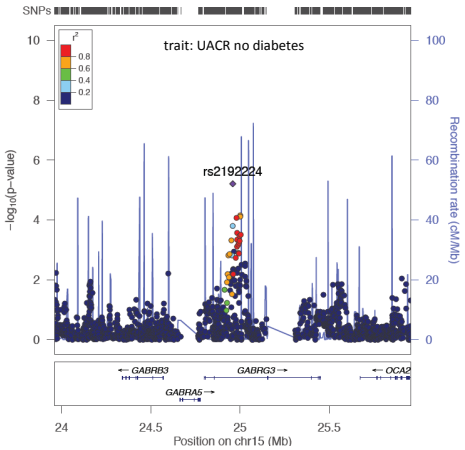

SNPs
trait: MA
rs6513791
−log10(p−value)
Recombination rate (cM/Mb)
CHD6 PTPRT
Position on chr20 (Mb)

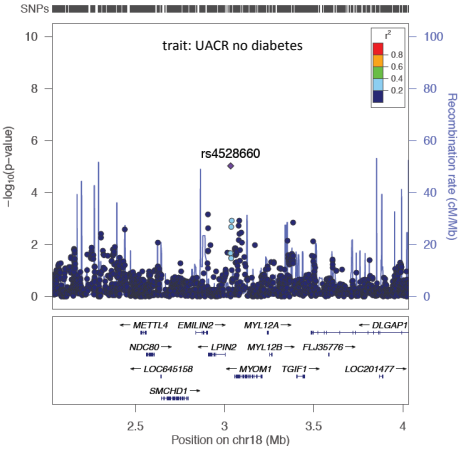

SNPs
trait: UACR no diabetes
rs17377079
−log10(p−value)
Recombination rate (cM/Mb)
TTLL7 SAMD13 SSX2IP MCOLN3 DDAH1
PRKACB RPF1 LPAR3 SYDE2 CYR61
UOX MCOLN2 BCL10 ZNHIT6
DNASE2B WDR63 COL24A1
Position on chr1 (Mb)

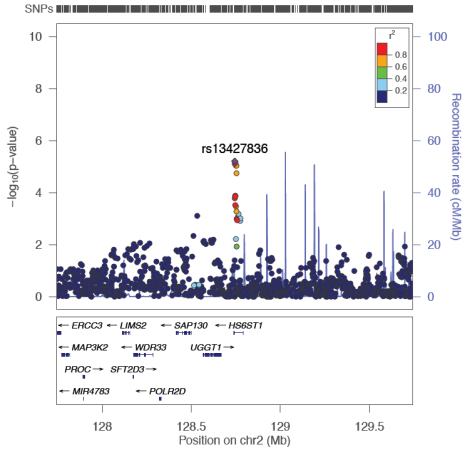

SNPs
trait: UACR no diabetes
rs4674086
−log10(p−value)
Recombination rate (cM/Mb)
SATB2 C2orf69 SPATS2L AOX2P NDUFB3
FLJ32063 TYW5 KCTD18 BZW1 CFLAR
FONG SGOL2 CLK1 CASP10
C2orf47 AOX1 PPIL3 CASP8
Position on chr2 (Mb)

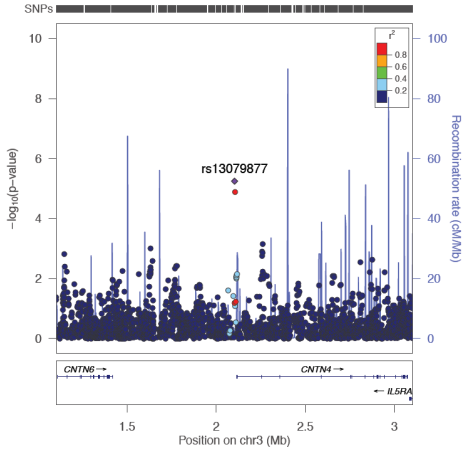

SNPs
trait: UACR no diabetes
rs9372872
−log10(p-value)
Recombination rate (cM/Mb)
RSPO3
C6orf174
THEMIS
PTPRK
RNF146
C6orf58
ECHDC1
KIAA0408
Position on chr6 (Mb)

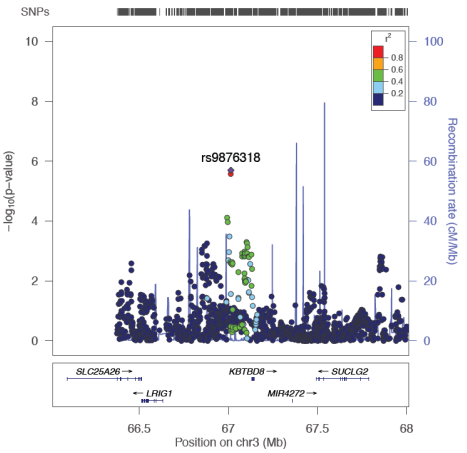

SNPs
trait: UACR no diabetes
rs12668467
−log10(p-value)
Recombination rate (cM/Mb)
SCIN
ETV1
DGKB
ARL4A
Position on chr7 (Mb)

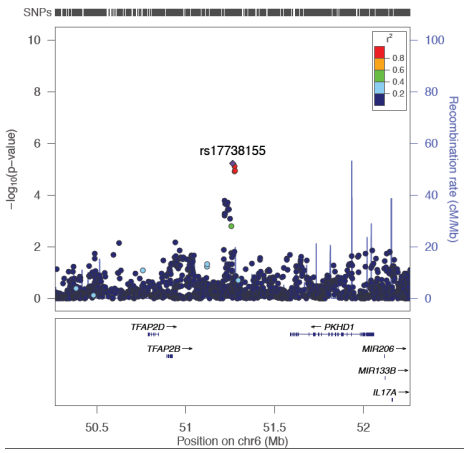

SNPs
trait: UACR no diabetes
rs2192224
−log10(p-value)
Recombination rate (cM/Mb)
GABRB3
GABRG3
OCA2
GABRA5
Position on chr15 (Mb)

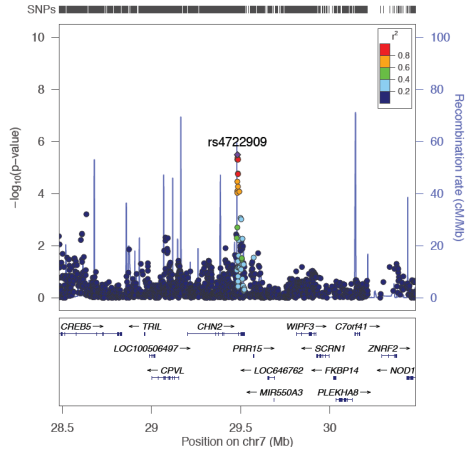

SNPs
trait: UACR no diabetes
rs4528660
−log10(p-value)
Recombination rate (cM/Mb)
METTL4
EMILIN2
MYL12A
DLGAP1
NDC80
LPIN2
MYL12B
FLJ35776
LOC645158
MYOM1
TGIF1
LOC201477
SMCHD1
Position on chr18 (Mb)

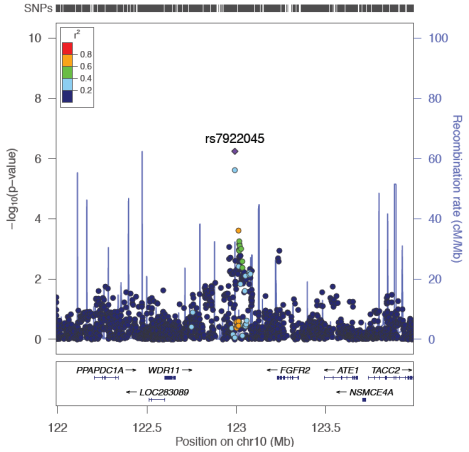

SNPs
rs13427836
ERCC3
LIMS2
SAP130
HS6ST1
MAP3K2
WDR33
UGGT1
PROC
SFT2D3
MIR4783
POLR2D
Position on chr2 (Mb)
Recombination rate (cM/Mb)

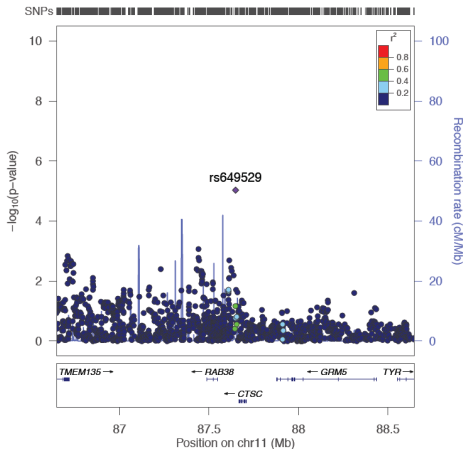

SNPs
rs13079877
CNTN6
CNTN4
IL5RA
Position on chr3 (Mb)
Recombination rate (cM/Mb)


SNPs
rs9876318
SLC25A26
KBTBD8
SUCLG2
LRIG1
MIR4272
Position on chr3 (Mb)
Recombination rate (cM/Mb)


SNPs
rs17738155
TFAP2D
TFAP2B
PKHD1
MIR206
MIR133B
IL17A
Position on chr6 (Mb)
Recombination rate (cM/Mb)

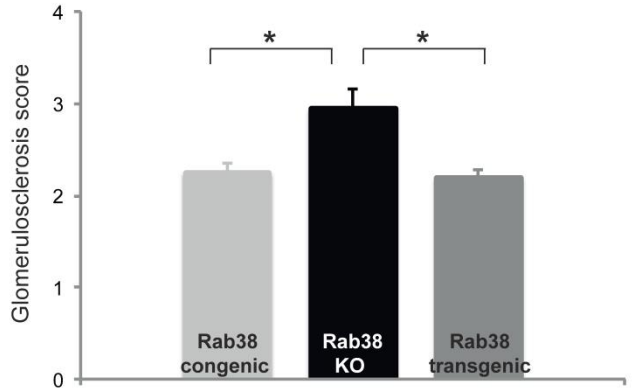

SNPs
rs4722909
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
CREB5 → ← TRIL CHN2 → WIPF3 → C7orf41 →
LOC100506497 → PRR15 → ← SCRN1 ZNRF2 →
← CPVL ← LOC646762 ← FKBP14 ← NOD1
← MIR550A3 PLEKHA8 →
28.5
29
29.5
30
Position on chr7 (Mb)

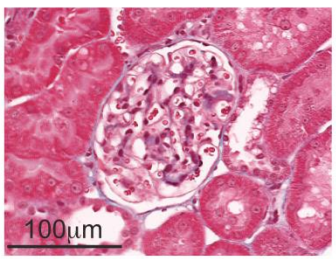

SNPs
rs7922045
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
PPAPDC1A → WDR11 → ← FGFR2 ← ATE1 TACC2 →
← LOC283089 ← NSMCE4A
122
122.5
123
123.5
Position on chr10 (Mb)


SNPs
rs649529
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
TMEM135 → ← RAB38 ← GRM5 TYR →
← CTSC
87
87.5
88
88.5
Position on chr11 (Mb)

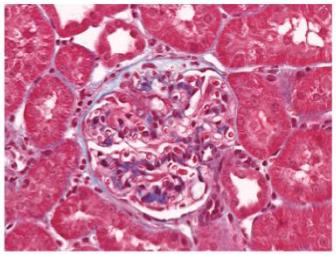
Supplementary Figure 4: Evaluation of glomerulosclerosis in Rab38 KO, congenic and transgenic rats.

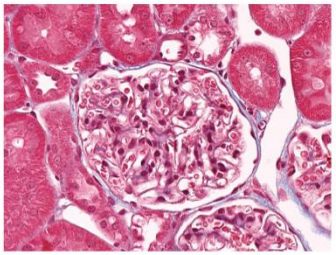
Representative images of trichrome-stained glomeruli from *Rab38* congenic, KO and transgenic animals. The glomerulosclerosis score was determined from left kidneys of 13-week-old rats (n=3 of each strain) as described previously (O'Meara CC *et al.* JASN, 2011). 50 to 60 40x magnified cortical glomeruli were imaged and scored, and scores were averaged for each animal. *p<0.05, **p<0.01 KO vs. transgenic, $^{\#\#}$p<0.01 KO vs. congenic. Glomerulosclerosis was analyzed using one-way ANOVA followed by Tukey's post hoc test.





Rab38 congenic


Rab38 KO


Rab38 transgenic

Supplementary Table 1: Characteristics of the study populations

Study	UACR sample size	Women, %	Age (years)	eGFR <60 (ml/min/1.73m^2)[1]	HTN, %	DM, %	UACR (mg/g) (median, 25th%, 75th%)	MA, %
Disovery cohorts								
3C	1072	63.6	77.8 (4.8)	19.9	74.4	12.3	5.3 (2.6, 10.7)	11.7
Advance	2203	32.8	66.7 (6.76)	14.7	47.6	100	15.6 (6.44, 54.8)	45
AGES	3196	58	76.4 (5.46)	24.2	80.6	11.5	2.66 (1.2, 7.0)	11.9
Amish**	727	48.9	49.5 (16.9)	3.1	18.9	1.7	7 (4.3, 13.5)	NA
ARIC	7243	53.1	61.8 (6.1)	8.7	40.7	14.2	5.3 (3.0, 9.5)	9.4
BLSA**	361	46.1	70.4 (15.2)	17.4	21.9	7.7	7 (4.4, 11.0)	NA
CHS	1865	61.3	71.9 (5.0)	9.5	51.4	11	9.3 (5.3, 19.9)	23
COLAUS	5311	53.2	53.4 (10.8)	3.8	36.1	9.6	5.1 (3.4, 9.1)	9.5
CROATIA-SPLIT**	472	59.8	49.3 (14.65)	5	39.4	5	2.5 (1.3, 5.8)	7.8
EPIC	2371	53.3	59.2 (9.00)	29.87	49.3	3	3.6 (1.5, 8.3)	8.1
Fenland**	1398	56.2	44.9 (7.3)	0.9	18.9	1.4	4.5 (3.2, 7.1)	5.5
FHS	6523	54.3	51.2 (14.0)	10.7	57.5	9.7	4.58 (2.62, 9.89)	9.69
INCIPE**	940	52.7	61.0 (11.0)	8.6	69.6	10.6	NA*	7.4
KORA-F3	1530	50.5	62.5 (10.1)	10.8	41.1	11.1	4.9 (2.1, 11.1)	12.5
KORA-F4	1804	51.3	60.9 (8.9)	7	20.9	9.2	6.1 (3.8, 11.9)	12.5
LIFELINES	8085	57.2	47.4 (11.2)	NA	31.5	2.2	3.12 (2.2, 4.7)	2.4
MESA	2511	52.3	62.67 (10.2)	9.72	38.6	5.99	4.60 (3.10, 8.50)	9.52
MICROS**	504	56.5	46.2 (16.1)	3.8	37.7	4.3	6.0 (4.0, 9.0)	5.4
PREVEND	3634	48.4	49.6 (12.5)	3.3	31.8	3.4	7.9 (5.0, 15.5)	10.2
SHIP	2655	51.7	54.5 (15.3)	7.7	51.1	11.2	8.95 (5.00, 20.59)	25.2
SHIP-TREND**	985	56.2	50.1 (13.7)	4.3	39.6	1.8	6 (3.9, 10.3)	8.5
Total	**55390**							

Replication cohorts								
ESTHER	2958	55.6	61.87	15.7	57.52	15.87	9.8 (6.2, 19.7)	23.06
GANI_MED	1674	44.0	60.0	36.1	71.2	24.9	11.8 (6.1, 43.9)	37.2
GENDIAN	450	47.1	65.05	32.3	53	100	7.54 (3.57,23.65)	27.6
KORAF4 non-GWAS	1195	52.4	49.2	5.8	13.3	4	5.7 (3.5, 11.4)	23.6
KORAF3 non-GWAS	1389	52.5	51.7	2.6	29.4	5.1	4.4 (1.87, 9.6)	11
SAPHIR	1690	37.1	51.4	6.9	55.7	3.3	3.8 (2.3, 8.3)	9.9
SKIPOGH**	807	52.3	47.1	5.7	22.9	4.5	4.2 (2.7, 7.7)	5.7
Vanderbilt Omni1	472	47.3	54.5	27.7	70.5	18	11.5 (6.0, 39.0)	36.7
Vanderbilt Omni5	144	46.9	50.5	21.7	58.2	33.3	14.5 (6.0, 42.2)	35.4
Vanderbilt 660W	365	56.5	56.5	20.6	57.2	17.9	9.0 (5.0, 26.0)	30.7
Total	**11144**							

*Because of the lower detection limit of the assay, the INCIPE Study only contributed to analyses of MA.
**Studies that did not contribute data for analyses of MA or UACR among those with diabetes because of low case numbers.
[1]Timepoint of serum creatinine measurement can differ from that of urinary albumin measurements in some of the studies.

Supplementary Table 2: Information about study design and UACR measurement

Study	Study Design	Total genotyped sample size	Study exclusions or disease enrichment, and data quality control	Urinary albumin measurements + QC	Key Study References
Discovery study					
3C	Prospective population-based	1072	**Study exclusions or disease enrichment**: none. **Exclusions**. none.	At 4-year follow-up, urinary albumin and creatinine were measured in a fresh morning urine sample in a single laboratory using an immunoturbidimetric assay for albumin and Jaffe method for creatinine.	1. The 3C Study Group. Vascular factors and risk of dementia. Design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology. 2003; 22:316-325. 2. Lambert J-C, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr B, Pasquier F, Fiévet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck F, Helisalmi S, Porcellini E, Hanon O, the European Alzheimer's Disease Investigators, De Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossù P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Galan P, Dartigues J-F, Tzourio C, Gut I, Van Broeckhoven C, Alpérovitch A, Lathrop M, Amouyel P. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet. 2009;41:1094-9.

Advance	Randomized controlled trial	2203	**Study exclusions or disease enrichment**: multicenter trial done by 215 collaborating centres in 20 countries, including 11,140 type 2 diabetes subjects all of Caucasian origin. **Exclusions**: 8829 with no genotype; 10 samples excluded due to sex mismatch, high sample missingness or having <0.8 of Caucasian ethnicity (STRUCTURE 2.3). Of the 2301 remaining samples of good genotype quality, 98 did not have data for UACR.	Urinary albumin and creatinine were measured in the same morning fresh sample in local certified laboratoires using local regulations in 20 countries. Units were harmonized centrally by the George Insitute. Two samples were required for the determination of the stage of albuminuria. UACR were repeated every 6 months during a 5-year follow-up.	1. Ninomiya T et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol. 2009 Aug;20(8):1813-21. 2. Patel A et al for the ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial). Lancet 2007; 370: 829-40.
AGES	Population-based	3196	**Study information or disease enrichment**: none. **Exclusions**: exclusion criteria included sample failure, genotype mismatch with reference panel, and sex mismatch, resulting in clean genotype data on 3,219 individuals.	Urinary albumin was measured in a morning urine sample using the Tina-quant immunoturbimetric assay (Roche Diagnostics, Mannheim). The intra-assay CV was 7.2%. Urinary creatinine in the same samples was measured using the HiCo Creatinine Jaffe method (Roche Diagnostics, Mannheim). The intra-assay CV was 4.2%.	Harris TB, Launer LJ, Eiriksdottir G, Kjartansson O, Jonsson PV, Sigurdsson G, Thorgeirsson G, Aspelund T, Garcia ME, Cotch MF, Hoffman HJ, Gudnason V.Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. Am J Epidemiol. 2007 May 1;165(9):1076-87.
Amish	Population-based "founder" cohort	727	**Study information or disease enrichment**: none. **Exclusions**: age < 20, severe chronic disease, call rate < 95%.	Urinary albumin concentration was measured from stored samples using a quantitative immunoturbimetric assay (Roche Diagnostics, Indianapolis), and creatinine in urine was measured using a modified Jaffe method.	1. Mitchell BD et al. The genetic response to short-term interventions affecting cardiovascular function: rationale and design of the Heredity and Phenotype Intervention (HAPI) Heart Study. Am. Heart J. 155, 823-828 (2008). 2. Rampersaud E et al. The association of coronary artery calcification and carotid artery intima-media thickness with distinct, traditional coronary artery disease risk factors in asymptomatic adults. Am. J. Epidemiol. 168, 1016-1023 (2008).

ARIC	Prospective, population-based	7243	**Study information or disease enrichment**: none. **Exclusions**: of the 9713 genotyped individuals of European ancestry, we excluded 658 individuals based on discrepancies with previous genotypes, disagreement between reported and genotypic sex, one randomly selected member of a pair of first-degree relatives, or outlier based on measures of average DST or more than 8 SD away on any of the first 10 principal components. Additional samples were excluded for this analysis because of the unavailability of the phenotype.	Using stored specimen from samples collected at visit 4, urinary albumin was measured by a nephelometric method either on the Dade Behring BN100 or on the Beckman Image Nephelometer. Urinary creatinine was measured using the Jaffe method.	The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol. 1989 Apr;129(4):687-702.
BLSA	Population-based	361	**Study information or disease enrichment**: none. **Exclusions**: non-European descent or with missing UACR information.	Urinary measurements were conducted on 24-hour urine samples. Urinary albumin was determined with nephelometry (Beckman Array System). Urinary creatinine was measured using a Vitros enzymatic assay (Johnson & Johnson Co., Rochester, NY).	Shock NW et al. Normal Human Aging: The Baltimore Study of Aging. 1984.
CHS	Prospective population-based	1865	**Study information or disease enrichment**: A total of 1908 persons were excluded from the GWAS study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack or lack of available DNA. **Exclusions**: The present report is based upon genotyping results from 3,329 CHS Caucasian participants, who were free of clinical cardiovascular disease at baseline, consented to genetic testing, and had DNA available for genotyping. Genotypes were called using the Illumina BeadStudio software. Genotyping was successful in 3,291 persons.	Urinary parameters were measured from a morning urine sample. The albumin was measured by rate nephelometry (Array 360 CE Protein Analyzer, Beckman Instruments, Fullerton, CA). The creatinine was measured using a Kodak Ektachem 700 Analyzer (Eastman Kodak company, Rochester, NY).	1. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol. 1991;1(3):263-276. 2. Heard-Costa, NL et al. NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. 2009. Plos Genet. 5(6): e1000539.

COLAUS	Population-based	5311	**Study exclusions or disease enrichment**: none. **Exclusions**: samples with call rate < 90% and related individuals.	Urinary albumin was measured using a Bromocresol green assay (Roche Diagnostics, Basel, Switzerland). The inter- and intra-assay CVs were 2.5% and 0.4%. Urinary creatinine was measured using a Jaffe kinetic compensated method. The inter- and intra-assay CVs were 2.9% and 0.7%.	Firmann M, Mayor V, Vidal PM, Bochud M, Pécoud A, Hayoz D, Paccaud F, Preisig M, Song KS, Yuan X, Danoff TM, Stirnadel HA, Waterworth D, Mooser V, Waeber G, Vollenweider P. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome.BMC Cardiovasc Disord. 2008 Mar 17;8:6. doi: 10.1186/1471-2261-8-6.
CROATIA-SPLIT	Population-based	472	**Study exclusions or disease enrichment**: none. **Exclusions**: missing UACR levels.	Urinary albumin excretion was measured, in stored urine samples, by an automated assay based on a turbimetric method with automatic calibration and quality control (Synchron CX System, Beckman Coulter).	"10001 Dalmatiians" Croatia launches its national biobank Rudan I, Marusić A, Janković S, Rotim K, Boban M, Lauc G, Grković I, Dogas Z, Zemunik T, Vatavuk Z, Bencić G, Rudan D, Mulić R, Krzelj V, Terzić J, Stojanović D, Puntarić D, Bilić E, Ropac D, Vorko-Jović A, Znaor A, Stevanović R, Biloglav Z, Polasek O.Croat Med J. 2009 Feb;50(1):4-6.
EPIC	Population-based	2371	**Study exclusions or disease enrichment**: participants taking colchicine, probenecid or allopurinol at 1st, 2nd health checks or 3rd follow-up; gout from hospital discharge ICD10 M10, between 1997-2008. **Exclusions**: none.	Urinary albumin was measured in spot urine by immunonephelometry using the Nephelometer II analyzer (Dade Behring, Marburg, Germany). The intra-assay CV was 2.91%. Urinary creatinine was measured by means of colorimetry using the Dimension AR Analyzer (Dade Behring Marburg, Germany).	1. Day N et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. Br J Cancer 80 Suppl 1, 95-103 (1999). 2. Lee CT et al. Cross-sectional association between fish consumption and albuminuria: the European Prospective Investigation of Cancer-Norfolk Study. Am J Kidney Dis 52, 876-86 (2008).
Fenland	Population-based	1398	**Study exclusions or disease enrichment**: exclusion criteria for the study were: age<30 or age>55, prevalent diabetes, pregnant and lactating women, inability to participate including terminal illness, psychotic illness, or inability to walk unaided. **Exclusions**: 102 exluded due to call rate < 95%, heterozygosity check (upper bound 0.2882, lower bound 0.2735), relatedness check and duplicate check.	Using stored samples, urinary albumin was measured by means of immunonephelometry using the Nephelometer II analyzer (Dade Behring, Marburg, Germany; intra-assay CV 2.91%). Urinary creatinine was measured through colorimetry using the Dimension AR Analyzer (Dade Behring Marburg, Germany).	Willer CJ, Speliotes EK, Loos RJ et al. (2009) Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet, 41(1): 25-34.

FHS	Prospective family-based	6523	**Study exclusions or disease enrichment**: none. **Exclusions**: Of the 9,274 participants who underwent genotyping, we made the following exclusions: sample call rate <97% (n=666), genotype heterozygosity > 5 standard deviations, and ambiguous family data (n=127). This resulted in a total of 8,481 genotyped individuals. Of them, 1958 did not have the phenotype available.	Urinary albumin was measured from stored samples using a Tina-quant immunoturbimetric assay (Roche Diagnostics, Indianapolis, Indiana). The intra-assay CV was 7.2% for the Offspring cohort and 2.1% for the Third Generation. Urinary creatinine was measured using a modified Jaffe method. Its intra-assay CV was 2.3% for the Offspring cohort and 1.0% for the Third Generation cohort.	1. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. Prev Med. 1975;4:518-525. 2. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. Am J Epidemiol. 1979;110:281-290. 3. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB, Sr., Fox CS, Larson MG, Murabito JM, O'Donnell CJ, Vasan RS, Wolf PA, Levy D. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. Am J Epidemiol. 2007;165:1328-1335.
INCIPE	Cross-sectional, population based	940	**Study exclusions or disease enrichment:** individuals <40 year old. **Exclusions:** pregnant women	Using stored specimen, urinary albumin was measured by a nephelometric method. Urinary creatinine was measured using the Jaffé method.	Gambaro, G. et al. Prevalence of CKD in northeastern Italy: results of the INCIPE study and comparison with NHANES. Clin. J. Am. Soc. Nephrol. 5, 1946-1953 (2010).
KORA-F3	Prospective population-based	1530	**Study exclusions or disease enrichment:** none**. Exclusions:** none.	Using stored urine samples, urinary albumin concentration was measured with a latex enhanced nephelometric assay (Siemens Healthcare Diagnostics) on a Dade Behring BN2 apparatus. Urinary creatinine concentration was measured using an enzymatic method.	1. Baumeister SE, Böger CA, Krämer BK, Doring A, Eheberg D, Fischer B, John J, Koenig W & Meisinger C: Effect of chronic kidney disease and comorbid conditions on health care costs: A 10-year observational study in a general population. Am J Nephrol 31: 222-229, 2010. 2. Wichmann HE, Gieger C & Illig T: KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. Gesundheitswesen 67 Suppl 1: S26-30, 2005.

KORA-F4	Prospective population-based	1804	**Study exclusions or disease enrichment**: none. **Exclusions**: none.	Using stored urine samples, urinary albumin concentration was measured with a latex enhanced nephelometric assay (Siemens Healthcare Diagnostics) on a Dade Behring BN2 apparatus. Urinary creatinine concentration was measured using a kinetic Jaffe method in KORA F4.	1. Baumeister SE, Böger CA, Krämer BK, Doring A, Eheberg D, Fischer B, John J, Koenig W & Meisinger C: Effect of chronic kidney disease and comorbid conditions on health care costs: A 10-year observational study in a general population. Am J Nephrol 31: 222-229. 2. Wichmann HE, Gieger C & Illig T: KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. Gesundheitswesen 67 Suppl 1: S26-30, 2005.
LIFELINES	3-generations, population-based	8085	**Study exclusions or disease enrichment**: living outside the 3 Northern provinces of The Netherlands. **Exclusions**: none.	Urinary albumin and creatinine were measured using the Roche Modular.	Stolk RP, Rosmalen JGM, Postma DS, de Boer RA, Navis G, Slaets JPJ, Ormel J, and Wolffenbuttel BHR. Universal risk factors for multifactorial diseases: LifeLines: a three-generation population-based study. Eur. J. Epidemiol., vol. 23, no. 1, pp. 67–74, Jan. 2008.
MESA	Community-based cohort study	2511	**Study exclusions or disease enrichment**: none. **Exclusions**: none.	Urine albumin and creatinine were measured at the Clinical Chemistry Laboratory at Fletcher Allen Health Care (Burlington, Vt). Urine albumin and creatinine were measured by nephelometry and the rate Jaffe reaction, respectively.	Bild DE et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 156, 871-81 (2002).

MICROS	Cross-sectional, population-based study using extended pedigrees	504	**Study exclusions or disease enrichment**: <18 years of age. **Exclusions**: samples with overall SNP call rate < 95%, showing excess of heterozygosity, or being classified as outliers by IBS clustering analysis were excluded prior to further analyses.	The urinary albumin-to-creatinine ratio was measured on a point-of-care diabetes management platform (Bayer DCA 2000+ analyzer).	1. Pattaro C, Marroni F, Riegler A, Mascalzoni D, Pichler I, Volpato CB, Dal Cero U, De Grandi A, Egger C, Eisendle A, Fuchsberger C, Gögele M, Pedrotti S, Pinggera GK, Stefanov SA, Vogl FD, Wiedermann CJ, Meitinger T, Pramstaller PP. The genetic study of three population microisolates in South Tyrol (MICROS): study design and epidemiological perspectives. BMC Med Genet. 2007;8:29. 2. Marroni F, Grazio D, Pattaro C, Devoto M, Pramstaller P. Estimates of genetic and environmental contribution to 43 quantitative traits support sharing of a homogeneous environment in an isolated population from South Tyrol, Italy. Hum Hered. 2008;65(3):175-82.
PREVEND	Population-based	3634	**Study exclusions or disease enrichment**: aged between 28-75 yrs, enriched for microalbuminuria. **Exclusions**: none.	Urinary albumin was determined from fresh urine samples by nephelometry (BNII; Dade Behring Diagnostic, Marburg, Germany). Intra- and inter-assay coefficients of variation were 2.2 and 2.6%, respectively.	Hillege HL, Fidler V, Diercks GFH, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans ROB, Janssen WMT, Grobbee DE, and de Jong PE. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation, vol. 106, no. 14, pp. 1777–82, Oct. 2002.
SHIP	Prospective population-based	2655	**Study exclusions or disease enrichment**: none. **Exclusions**: sample call rate < 92%, duplicate samples (by IBS estimation), individuals with reported / genotyped gender mismatch.	Urinary albumin was measured from spot first morning void urine by nephelometry (BNII, Dade Behring Diagnostica, Marburg, Germany). Intra-assay and interassay coefficients of variation were 4.3% and 4.4%, respectively. Urinary creatinine concentration was measured using Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY). Intra-assay and interassay coefficients of variation were 0.9% and 2.9%, respectively.	1. John U et al. Study of Health in Pomerania (SHIP). A health examination in an east German region: objectives and design. Soz Praventivmed 46:186-194, 2001. 2. Völzke H et al. Cohort Profile: The Study of Health in Pomerania. Int J Epidemiol, vol. 40, no. 2, pp. 294–307, Apr. 2011.

SHIP-TREND	Prospective population-based	985	**Study exclusions or disease enrichment**: this analysis concerns the subset of 988 individuals with genotype information. **Exclusions**: sample call rate < 94%, duplicate samples (by IBS estimation), individuals with reported/genotyped gender mismatch.	In a sample of spot urine, both the urinary albumin (intra-assay CV 4.5-7.6% for 1.0-24.5 mg/dl) and creatinine (Jaffe method, intra-assay CV 1.4-2.1% for 5.7-14.6 mmol/l) were measured on a Siemens Dimension Vista 1500 analyzer (Siemens Healthcare Diagnostics, Marburg, Germany), respectively.	1. John U et al. Study of Health in Pomerania (SHIP). A health examination in an east German region: objectives and design. Soz Praventivmed 46:186-194, 2001. 2. Völzke H et al. Cohort Profile: The Study of Health in Pomerania. Int J Epidemiol, vol. 40, no. 2, pp. 294–307, Apr. 2011.
Replication study					
ESTHER	Prospective study	2958	**Study exclusions or disease enrichment**: study participants were required to be ≥50 year old and having a good knowledge of the German language. **Exclusions**: samples with insufficient amount of DNA for genotyping.	Urinary albumin concentration was measured using nephelometric method (Siemens. Marburg, Germany). The urinary creatinine levels were photometrically measured using the modified kinetic Jaffe method (Greiner Diagnostic GmbH. Bahlingen, Germany).	1. Raum E, Rothenbacher D, Low M, Stegmaier C, Ziegler H, Brenner H. Changes of cardiovascular risk factors and their implications in subsequent birth cohorts of older adults in Germany: a life course approach. Eur J Cardiovasc Prev Rehabil 2007;14:809-814. 2. Schottker B, Haug U, Schomburg L, et al. Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study. Am J Clin Nutr 2013. 3. Weck MN, Stegmaier C, Rothenbacher D et al. Epidemiology of chronic atrophic gastritis: population-based study among 9444 older adults from Germany. Aliment Pharmacol Ther. 2007;26:879-887.
GANI_MED	Cohort study	1674	**Study exclusions or disease enrichment**: six main cohorts: heart failure, stroke, periodontal disease, renal insufficiency, metabolic syndrome, and fatty liver disease. **Exclusions:** sample call rate < 94%, heterozygosity rate > 6SD (MAF > 1%), PCA outliers (EV 1-4 > 8SD), duplicate samples (by IBS estimation), individuals with reported/genotyped gender mismatch..	In a sample of spot urine, the urinary albumin was measured on a Siemens Dimension Vista 1500 analyzer (Siemens Healthcare Diagnostics, Marburg, Germany). Urinary creatinine was measured either by an enzymatic or Jaffe method, whereas the analyses were adjusted accordingly for the method used.	Grabe HJ, Assel H, Bahls T et al. Cohort profile: Greifswald approach to individualized medicine (GANI_MED). J. Transl. Med. 2014; 12: 144.

GENDIAN	Cohort study	450	**Study exclusions or disease enrichment**: study on type 2 diabetes patients. **Exclusions**: of the 1,026 subjects undergoing genotyping, 53 were excluded due to call-rate < 95% (n=22), relatedness and duplicates (n=11), gender mismatch (n=16), ethnicity check (n=4); in addition, we excluded the following patients for the current analysis of cross-sectional UACR: patients with end-stage renal disease (n=438) or advanced, histologically proven diabetic nephropathy (n=84) or missing phenotype (n=1).	Urinary creatinine was measured using an enzymatic assay, urinary albumin was measured using the Roche Tina Quant assay.	1. Böger CA et al: effect of ACE and AT-2 inhibitors on mortality and progression to microalbuminuria in a nested case control study of diabetic nephropathy in diabetes mellitus type 2: results from the GENDIAN study. Int J Clin Pharmacol Ther 2006;44:364-74. 2. Böger CA et al. Association of eGFR-related loci identified by GWAS with incident CKD and ESRD. Plos Genet 2011;7:e1002292.
KORAF4 non-GWAS	Prospective population-based	1195	**Study exclusions or disease enrichment**: none. **Exclusions**: none.	Using stored urine samples, urinary albumin concentration was measured with a latex enhanced nephelometric assay (Siemens Healthcare Diagnostics) on a Dade Behring BN2 apparatus. Urinary creatinine concentration was measured using an enzymatic method.	1. Baumeister SE, Böger CA, Krämer BK, Doring A, Eheberg D, Fischer B, John J, Koenig W & Meisinger C: Effect of chronic kidney disease and comorbid conditions on health care costs: A 10-year observational study in a general population. Am J Nephrol 31: 222-229, 2010. 2. Wichmann HE, Gieger C & Illig T: KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. Gesundheitswesen 67 Suppl 1: S26-30, 2005.
KORAF3 non-GWAS	Prospective population-based	1389	**Study exclusions or disease enrichment**: none. **Exclusions**: none.	Using stored urine samples, urinary albumin concentration was measured with a latex enhanced nephelometric assay (Siemens Healthcare Diagnostics) on a Dade Behring BN2 apparatus. Urinary creatinine concentration was measured using a kinetic Jaffe method in KORA F4.	1. Baumeister SE, Böger CA, Krämer BK, Doring A, Eheberg D, Fischer B, John J, Koenig W & Meisinger C: Effect of chronic kidney disease and comorbid conditions on health care costs: A 10-year observational study in a general population. Am J Nephrol 31: 222-229, 2010. 2. Wichmann HE, Gieger C & Illig T: KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. Gesundheitswesen 67 Suppl 1: S26-30, 2005.

SAPHIR	Healthy working population	1690	**Study exclusions or disease enrichment**: none. **Exclusions**: none.	Urinary creatinine was measured using a modified kinetic Jaffe reaction (CREA, Roche Diagnostics GmbH, Mannheim, Germany). Urinary albumin concentration was determined using the Tinaquant assay (Roche Diagnostics GmbH, Mannheim, Germany).	1. Heid IM, Wagner SA, Gohlke H, Iglseder B, Mueller JC, Cip P, Ladurner G, Reiter R, Stadlmayr A, Mackevics V, Illig T, Kronenberg F, Paulweber B: Genetic architecture of the APM1 gene and its influence on adiponectin plasma levels and parameters of the metabolic syndrome in 1,727 healthy Caucasians. Diabetes 55:375-384, 2006. 2. Kollerits B, Coassin S, Kiechl S, Hunt SC, Paulweber B, Willeit J, Brandstätter A, Lamina C, Adams TD, Kronenberg F: A common variant in the adiponutrin gene influences liver enzyme levels. Journal of Medical Genetics 47:116-119, 2010.
SKIPOGH	Cross-sectional family-based population-based	807	**Study exclusions or disease enrichment**: none. **Exclusions**: of the 941 participants who underwent genotyping, we excluded 71 participants with call rate < 90%, resulting in a total of 870 genotyped individuals.	Urinary creatinine was measured using an IDMS-traceable Jaffe kinetic compensated method. Urinary albumin concentration was measured using a quantitative immuno-nephelometry.	Pruijm M, Ponte B, Ackermann D, Vuistiner P, Paccaud F, Guessous I, Ehret G, Eisenberger U, Mohaupt M, Burnier M, Martin PY, Bochud M. Eur Radiol. 2013 May 28. [Epub ahead of print].
Vanderbilt Omni1	Practice-based cohort	472	**Study exclusions or disease enrichment**: samples chosen based on being a case or control for one of 31 pharmacogenetic analyses. **Exclusions**: individuals of non-white ancestry in the electronic medical record. Also excluded any lab measurements of individuals after initiation of dialysis or a kidney transplant.	The urinary albumin concentration was measured using turbidimetric immunoassay with endpoint determination. Urinary creatinine levels were measured using the modified Jaffé method.	
Vanderbilt Omni5	Practice-based cohort	144	**Study exclusions or disease enrichment**: samples chosen based on being a case or control for one of 31 pharmacogenetic analyses. **Exclusions**: individuals of non-white ancestry in the electronic medical record. Also excluded any lab measurements of individuals after initiation of dialysis or a kidney transplant.	The urinary albumin concentration was measured using turbidimetric immunoassay with endpoint determination. Urinary creatinine levels were measured using the modified Jaffé method.	

Vanderbilt 660W	Practice-based cohort	365	**Study exclusions or disease enrichment**: samples chosen for normal cardiac conduction, meaning that at some point in time they had a normal electrocardiogram without the presence of heart disease, arrhythmias, or electrocardiographically-active medications. **Exclusions**: children (age <18) and individuals of non-white ancestry in the electronic medical record. Also excluded any lab measurements from individuals after initiation of dialysis or a kidney transplant. At some point in their electronic medical record, the patients were absent of heart disease, but could later develop it.	The urinary albumin concentration was measured using turbidimetric immunoassay with endpoint determination. Urinary creatinine levels were measured using the modified Jaffé method.	Denny JC, Ritchie MD, Crawford DC, Schildcrout JS, Ramirez AH, Pulley JM, Basford MA, Masys DR, Haines JL, Roden DM. Identification of genomic predictors of atrioventricular conduction: Using electronic medical records as a tool for genome science. Circulation 2010;122(20):2016-21.
Clinical characterization study					
DCCT/EDIC	Trial of patients with type I diabetes	1304	**Study exclusions or disease enrichment**: individuals with insulin-dependent type I diabetes mellitus between 1 and 15 years of duration, age 13-39 years at enrolment, free of advanced diabetes-related complications, absence of several comorbidities. **Exclusions**: Subjects meeting the criteria for persistent microalbuminuria at DCCT baseline and DCCT year 1 (n = 60) were excluded from the analyses of the time to incident albuminuria. Analyses were restricted to individuals of European ancestry.	The urinary albumin concentration was measured from times urine samples using a solid-phase fluoroimmunoassay. Urinary creatinine levels were measured using the Jaffé method.	1. The Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. Kidney Int 1995;47(6):1703–20. 2. de Boer IH et al. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med. 2011 Mar 14;171(5):412-20.

Supplementary Table 3: Study-specific information about genotyping, imputation and data management and analysis

Study Name	Genotyping Array type	Genotype calling algorithm	QC filters for genotyped SNPs used for imputation (listed are criteria for exclusion)	No of SNPs used for imputation	Imputation software, version	Imputation Backbone (NCBI build)	Filtering of imputed genotypes	Data management and statistical analysis
3C	Illumina Human610-Quad	BeadStudio	call rate < 98%, pHWE < 10E-6, MAF < 1%	492,897	MACH	1000 Genomes EUR, Dec 2010 (Build 37)	none	R and ProbABEL
Advance	Affymetrix 5.0 Affymetrix 6.0	Affymetrix	SNPs genotyped on Affymetrix 5.0: call rate < 96% (<99% if MAF < 5%); SNPs genotyped on Affymetrix 6.0: call rate < 97% (<99% if MAF < 5%)	876,688	IMPUTE2 2.1.2	1000 Genomes CEU Pilot, Jun 2010 plus HapMap 3 rel. 2 all available haplotypes, Feb 2009 (build 36)	imputation info < 0.5	SNPTEST
AGES	Illumina Hu370CNV	Illumina	call rate < 97%, pHWE < 1e-6, MAF < 0.01, mishap p < 1e-9, SNPs not in Hapmap or strandedness issues merging with Hapmap	329,804	MACH 1.0.16	HapMap rel. 22 (build 36)	none	R,ProbABEL, Linear and Logistic Regression
Amish	Affymetrix 500K	BRLMM	call rate < 95%, pHWE < 10E-6, MAF < 1%, non-HapMap	338,598	MACH 1.0.15	HapMap rel. 22 phased CEU haplotypes (build 36)	none	Measured genotype accounting for polygenic component
ARIC	Affymetrix 6.0	Birdseed	call rate < 95%, pHWE < 10E-5, MAF < 1%	669,450	MACH 1.0.16	HapMap rel. 22 (build 36)	none	ProbABEL, PLINK, R
BLSA	Illumina Infinium HumanHap 550K	Beadstudio	call rate < 99%, pHWE < 10E-4, MAF < 1%	501,764	MACH 1.0.15	HapMap rel. 21 phased CEU haplotypes (build 35)	MAF < 1%, r2hat < 0.3	SAS, Merlin, R
CHS	Illumina 370CNV	BeadStudio	call rate<97%, pHWE<10E-5, heterozygotes=0, SNP not in HapMap	306,655	BimBam 0.99	HapMap rel. 22 (build 36)	dosage variance<0.01	Linear and logistic regression using R, robust estimates of SE
COLAUS	Affymetrix 500K	BRLMM	call rate < 70%, pHWE < 10E-7	390,631	IMPUTE 0.2.0	HapMap rel. 21 (build 35)	none	Matlab
CROATIA-SPLIT	HAP370CNV	Illumina	call rate < 98%, pHWE < 10E-10	330,997	MACH 1.0.15	HapMap rel. 22 CEU haplotypes (build 36)	none	R(GenABEL, ProABEL)
EPIC	Affymetrix 500K	BRLMM	call rate < 90%, pHWE < 10e-6	382,037	IMPUTE 0.3.1	HapMap rel. 21 (Build 35)	none	SAS, Stata, Linux scripts
Fenland	Affymetrix 500K	BRLMM	call rate < 90%, pHWE < 10E-6, MAF < 1%	362,055	IMPUTE 0.4.2	HapMap rel. 22 (build 36)	proper_info<0.4	Linux, Stata 10.1, SNPTEST 1.1.5
FHS	Affymetrix 500K Affymetrix 50K	Affymetrix	call rate < 95%, pHWE < 10E-6	503,526	MACH 1.0.15	HapMap rel. 22 phased CEU haplotypes (build 36)	none	R

	supplemental							
INCIPE	Illumina	Illumina	call rate < 95%, pHWE < 10E-6	635,646	IMPUTE 0.2.0	HapMap rel. 22 phased CEU haplotypes (build 36)	none	R
KORA-F3	Affymetrix 500K	BRLMM	per-chip call rate < 93%, MAF < 5%,discrepancy for one of the 50 SNPs common on both chips, gender checks	380,407	MACH	HapMap rel. 22 (build 35)	none	MACH2QTL, ProbABEL, R, Visual Basic
KORA-F4	Affymetrix 6.0	BRLMM	per-chip call rate < 93%, per SNP call rate < 93%, MAF < 1%, gender checks	629,893	MACH	HapMap rel. 22 (build 36)	none	MACH2QTL, ProbABEL, R, Visual Basic
LIFELINES	Illumina CytoSNP12 v2	GenomeStudio	call rate < 95%, pHWE < 1E-05	257,581		HapMap rel. 22 phased CEU haplotypes (build 36)	none	NO
MESA	Affymetrix Genome-Wide Human SNP Array 6.0	Birdseed v2	call rate < 95%, MAF ≤ 1%	897,979	IMPUTE 2.1.0	HapMap rel. 22 phased CEU haplotypes (build 36)	none	PLINK
MICROS	Illumina Infinium HumanHap300 v2 SNP bead microarrays	Beadstudio	call rate < 98%, pHWE < 10E-6, MAF < 1%	292,917	MACH 1.0.16	HapMap rel. 22 (build 36)	none	R, GenABEL, ProbABEL;
PREVEND	Illumina CytoSNP12 v2	GenomeStudio	call rate < 95%, pHWE < 1E-05	232,571		HapMap rel. 22 phased CEU haplotypes (build 36)	none	NO
SHIP	Affymetrix 6.0	Birdseed2	none	869,224	IMPUTE 0.5.0	HapMap rel. 22 (build 36)	none	SNPTEST 1.1.5, QUICKTEST 0.94, R, InforSense, InterSystems Caché
SHIP-TREND	Illumina Human Omni 2.5	GenomeStudio	call rate ≤ 0.9, pHWE ≤ 1E-04, monomorphic SNPs	1,782,967	IMPUTE 2.1.2.3	HapMap rel. 22 phased CEU haplotypes (build 36)	duplicate RSID but different positions	QUICKTEST 0.95, R, InforSense, InterSystems Caché
***in silico* replication**								
GANI_MED	Illumina Infinium PsychArray	GenomeStudio	call rate ≤ 0.95, pHWE ≤ 1E-04, MAF ≤ 0.005	305,145	IMPUTE 2.3.1	1000 Genomes Phase I v3 ALL (macGT1) (build 37)	duplicate IDs (via positions)	R, PLINK, gtool, InterSystems Caché
GENDIAN	Genome-Wide Human SNP Array 6.0	Birdseed (BRLMM)	n=126,259 SNPs (chr 1-chr22, chr X) were excluded from imputation by SNP QC due to one of the following: HWE-p < 10-6; monomorphic SNPs; MAF>.1 & call rate<.9 MAF>.09 & MAF <=.1 & call rate<.91 MAF>.08 & MAF <=.09 & call rate<.92	747,402	MACH 1.0.18.c MiniMac 2012-10-09	GIANT ALL 1000G v3 ref panel GRCh (build 37)	none	R

			MAF>.07 & MAF <=.08 & call rate<.93 MAF>.06 & MAF <=.07 & call rate<.94 MAF>.05 & MAF <=.06 & call rate<.95 MAF>.04 & MAF <=.05 & call rate<.96 MAF>.03 & MAF <=.04 & callr ate<.97 MAF>.02 & MAF <=.03 & call rate<.98 MAF>.01 & MAF <=.02 & call rate<.99 MAF <=.01 & call rate<.99					
Vanderbilt Omni1	Illumina HumanOmni1-Quad	BeadStudio	call rate < 98%, IBD (Z0<0.8), Mendel errors > 0, Duplicate concordance < 100%	946,523	IMPUTE 2.3.0	1000 Genomes Phase 1 integrated v3	Genotype Likelihood <0.9	Plink and R
Vanderbilt Omni5	Illumina HumanOmni5-Quad	BeadStudio	call rate < 98%, IBD (Z0<0.8), Mendel errors > 0, Duplicate concordance < 100%	3,819,154	IMPUTE 2.3.0	1000 Genomes Phase 1 integrated v3	Genotype Likelihood <0.9	Plink and R
Vanderbilt 660W	Illumina Human660W-Quad	BeadStudio	call rate < 98%, IBD (Z0<0.8), Mendel errors > 0, Duplicate concordance < 100%	530,014	IMPUTE 2.3.0	1000 Genomes Phase 1 integrated v3	Genotype Likelihood <0.9	Plink and R
***de novo* replication**								
	genotyping platform	**amount of DNA used per SNP (in ng)**	**genotyping method**	**n duplicates and concordance per SNP (provide per individual SNP)**	**number attempted /number genotyped (per individual SNP)**	**Other QC indices that your lab uses**		
ESTHER	LGC genomics SNP-line, using KASP Chemistry and 1536-well plates	3.75	De novo genotyping using KASPar v4.0 after whole genome amplification by primer extension preamplification (PEP) using thermostable DNA polymerases	LGC Genomics does not add duplicates. The data for each SNP represents one reaction per sample.	call rate range 0.98 - 1	none indicated by the lab		
SKIPOGH	LGC genomics SNP-line, using KASP Chemistry and 1536-well plates	5 -7.5	De novo genotyping using KASPar v4.0 after whole genome amplification by primer extension preamplification (PEP) using thermostable DNA polymerases	29 participants were genotyped in duplicate. SNP concordance	SNP call rates varied from 94.5% to 99.5% (median 97.2)	All assays have been validated on an in-house DNA panel (44 random Caucasian DNA samples). All sample plates genotyped include at least two negative controls. ie.		

				varied between 86% and 100%.		blank/water controls. All genotyping data are initially generated by an automated algorithm (genotype calling based upon recorded fluorescence values). All genotyping data is manually checked and verified by no less than two experienced scientists at LGC genomics.		
KORAF4 non-GWAS	Mass ARRAY Analyzer 4 system	15	iPlex Gold	At least 15% duplicate genotyping per SNP. Concordance≥95%, median = 100%	NA	NA		
KORAF3 non-GWAS	Mass ARRAY Analyzer 4 system	15	iPlex Gold	At least 15% duplicate genotyping per SNP. Concordance≥95%, median = 100%	NA	NA		
SAPHIR	Mass ARRAY Analyzer 4 system	15	iPlex Gold	70 duplicates; 46 SNPs were genotyped; 44 SNPs had a concordance of 100%; 2 SNPs had each 1 discordant sample	46 SNPs were genotyped and had an aerage callrate of 99,3% (between 98.15% and 99.65%)	automatic calculation of the HWE, comparison of the obtained genotypes with HapMap Data		

Supplementary Table 4: SNPs associated with UACR among all individuals with a p-value of <1E-05.

SNPID	chr	position (hg18)	Allele1	Allele2	Frequency Allele1	Effect	SE	p-value	I^2 %	Sample Size	In Gene	Genes Within 100kb
rs880315	1	10719453	t	c	0.65	-0.042	0.009	9.1E-06	0	41333	*CASZ1*	
rs4072037	1	153428691	t	c	0.54	0.029	0.006	2.5E-06	0	54450	*MUC1*	MIR92B(dist=2901),THBS3(dist=3312),TRIM46(dist=4620),KRTCAP2(dist=16263),MTX1(dist=16423),GBAP1(dist=21549),GBA(dist=42172),DPM3(dist=49071),SLC50A1(dist=50733),EFNA1(dist=54681),FAM189B(dist=54929),SCAMP3(dist=63703),CLK2(dist=70592),HCN3(dist=85151),PKLR(dist=97017)
rs914615	1	153442516	a	g	0.47	-0.030	0.007	7.4E-06	0	44877	*THBS3*	MTX1(dist=2598),GBAP1(dist=7724),MIR92B(dist=10829),MUC1(dist=13186),TRIM46(dist=18445),GBA(dist=28347),KRTCAP2(dist=30088),FAM189B(dist=41104),SCAMP3(dist=49878),CLK2(dist=56767),DPM3(dist=62896),SLC50A1(dist=64558),EFNA1(dist=68506),HCN3(dist=71326),PKLR(dist=83192)
rs17346504	2	137640231	t	c	0.12	0.050	0.011	7.2E-06	27	53401	*THSD7B*	
rs9333289	2	187206352	t	c	0.70	-0.030	0.007	9.3E-06	24	54441	*ITGAV*	FAM171B(dist=60682)
rs9333290	2	187227583	t	g	0.30	0.038	0.008	7.5E-07	15	54441	*ITGAV*	FAM171B(dist=39451)
rs13006483	2	187230995	t	g	0.30	0.037	0.008	1.2E-06	15	54441	*ITGAV*	FAM171B(dist=36039)
rs3816386	2	187236880	a	g	0.69	-0.035	0.007	2.9E-06	0	54441	*ITGAV*	FAM171B(dist=30154)
rs11685758	2	187241613	t	c	0.31	0.039	0.008	2.7E-06	0	44877	*ITGAV*	FAM171B(dist=25421)
rs12151442	2	187246092	t	c	0.70	-0.030	0.007	5.5E-06	1	54441	*ITGAV*	FAM171B(dist=20942)
rs13001028	2	187255140	a	g	0.69	-0.035	0.007	2.0E-06	0	54440		ITGAV(dist=1266),FAM171B(dist=11894)
rs13028817	2	187255744	t	g	0.70	-0.029	0.007	7.3E-06	0	54439		ITGAV(dist=1870),FAM171B(dist=11290)
rs12615659	2	187259552	a	t	0.30	0.030	0.007	4.3E-06	2	54439		ITGAV(dist=5678),FAM171B(dist=7482)
rs11678190	2	187268553	a	c	0.69	-0.036	0.007	1.5E-06	0	54441	*FAM171B*	ITGAV(dist=14679)
rs17750683	2	187328542	a	t	0.68	-0.033	0.007	4.1E-06	22	54439	*FAM171B*	ZSWIM2(dist=71910),ITGAV(dist=74668)
rs13026081	2	187334583	t	c	0.32	0.032	0.007	6.8E-06	21	54434	*FAM171B*	ZSWIM2(dist=65869),ITGAV(dist=80709)
rs11783652	8	55021047	a	g	0.32	0.037	0.008	2.4E-06	0	54450	*RGS20*	TCEA1(dist=20620)
rs17301329	8	55021534	a	t	0.29	0.042	0.008	5.6E-07	0	54450	*RGS20*	TCEA1(dist=20133),LYPLA1(dist=99946)
rs16919699	8	55021582	t	c	0.66	-0.037	0.008	2.3E-06	0	54450	*RGS20*	TCEA1(dist=20085),LYPLA1(dist=99898)
rs1016013	9	96516305	a	g	0.42	0.028	0.006	6.4E-06	5	54450		C9orf3(dist=12467),FBP1(dist=73953),MIR2278(dist=95760)
rs7851726	9	96543806	t	c	0.42	0.027	0.006	5.2E-06	3	54450	*C9orf3*	MIR2278(dist=68259)
rs446540	9	96549020	a	g	0.43	0.028	0.006	5.8E-06	10	54304	*C9orf3*	MIR2278(dist=63045)
rs183066	9	96557253	t	c	0.57	-0.028	0.006	5.8E-06	9	54448	*C9orf3*	MIR2278(dist=54812)
rs2584806	9	96569099	a	c	0.58	-0.027	0.006	9.3E-06	9	54449	*C9orf3*	MIR2278(dist=42966)
rs1109861	10	11286275	a	c	0.55	-0.030	0.006	1.9E-06	5	54442	*CELF2*	CELF2-AS2(dist=98818)
rs1801239	10	16959058	t	c	0.90	-0.066	0.011	4.6E-09	31	54450	*CUBN*	RSU1(dist=59599)

rs17343073	10	16972202	a	t	0.90	-0.071	0.012	4.0E-09	22	54449	*CUBN*	RSU1(dist=72743)
rs6602163	10	17006772	a	g	0.84	-0.056	0.009	1.2E-09	5	54450	*CUBN*	
rs10795433*	10	17009929	a	c	0.86	-0.061	0.010	2.4E-10	6	54450	*CUBN*	
rs2417849	12	20167780	t	c	0.37	0.028	0.006	9.5E-06	39	54441		LOC100506393(dist=24711)
rs2303658	12	20169697	a	g	0.34	0.030	0.007	9.5E-06	31	54442		LOC100506393(dist=26628)
rs11609944	12	20170557	a	g	0.38	0.028	0.006	9.6E-06	42	54449		LOC100506393(dist=27488)
rs1728897	15	53088662	t	c	0.54	-0.028	0.006	4.1E-06	0	54433		
rs12594729	15	53088684	a	g	0.50	0.029	0.006	2.0E-06	0	54450		
rs7167661	15	53090751	t	c	0.54	-0.028	0.006	3.5E-06	0	54450		
rs11071163	15	53091242	a	g	0.50	-0.029	0.006	9.2E-06	0	54449		
rs7173577	15	53092295	a	g	0.45	-0.029	0.006	2.3E-06	0	54450		
rs1728867	15	53094106	a	g	0.45	-0.030	0.006	8.3E-07	0	54449		
rs951048	15	53094503	a	t	0.44	-0.030	0.006	8.7E-07	0	54449		
rs2414396	15	53094680	a	g	0.46	-0.031	0.006	7.6E-07	0	54449		
rs12907410	15	53095223	t	c	0.56	0.028	0.006	3.7E-06	0	54449		
rs1728886	15	53095714	t	c	0.56	0.030	0.006	1.2E-06	0	54449		
rs17818939	15	53096140	a	g	0.44	-0.030	0.006	1.1E-06	0	54450		
rs1728878	15	53097144	t	c	0.57	0.028	0.006	1.9E-06	0	54450		
rs8042768	15	53097375	a	g	0.43	-0.028	0.006	2.1E-06	0	54448		
rs1690363	15	53098119	a	g	0.43	-0.028	0.006	2.0E-06	0	54448		
rs1690365	15	53098549	t	c	0.56	0.028	0.006	1.9E-06	0	54450		
rs1614271	15	53098677	t	c	0.57	0.029	0.006	1.6E-06	0	54448		
rs1690366	15	53098855	t	g	0.44	-0.030	0.006	2.0E-06	0	54448		
rs1690367	15	53099066	a	g	0.43	-0.028	0.006	1.8E-06	0	54406		
rs7180127	15	53103432	t	c	0.51	0.029	0.006	3.7E-06	0	54449		
rs10083619	15	53106962	a	g	0.51	0.029	0.006	3.5E-06	0	54448		
rs2899576	15	53107909	t	c	0.48	-0.030	0.006	1.2E-06	0	54424		
rs1528472	15	53108420	a	c	0.48	-0.032	0.006	5.4E-07	0	54445		
rs17238122	15	53109188	a	g	0.48	-0.031	0.006	8.8E-07	0	54443		
rs1528477	15	53111680	a	g	0.48	-0.031	0.006	1.5E-06	0	54449		
rs1830324	15	53112207	a	g	0.51	-0.030	0.006	3.4E-06	0	54449		
rs11858741	15	53112699	a	g	0.51	0.030	0.006	2.2E-06	0	54450		
rs231226	19	40959617	t	c	0.62	-0.033	0.007	5.1E-06	22	44877	*ARHGAP33*	PROSER3(dist=7700),LINC01529(dist=12001),HSPB6(dist=19847),LIN37(dist=22357),PRODH2(dist=23115),PSENEN(dist=29721),U2AF1L4(dist=31434),IGFLR1(dist=34426),KMT2B(dist=37996),NPHS1(dist=48497),ZBTB32(dist=59837),KIRREL2(dist=80033),APLP1(dist=91624),UPK1A(dist=98390)
rs231227	19	40959907	a	g	0.38	0.033	0.007	4.9E-06	22	44877	*ARHGAP33*	PROSER3(dist=7990),LINC01529(dist=11711),HSPB6(dist=20137),LIN37(dist=22647),PRODH2(dist=22825),PSENEN(dist=30011),U2AF1L4(dist=31724),IGFLR1(dist=34716),KMT2B(dist=38286),NPHS1(dist=48207),ZBTB32(dist=60127),KIRREL2(dist=79743),APLP1(dist=91334),UPK1A(dist=98680)

rs2828785	21	24359376	t	c	0.27	-0.038	0.008	7.9E-06	0	54450

Standard error (SE) and p-values are corrected for genomic control. A1 is the coded allele.

*The previously identified missense variant rs18012399 in *CUBN* is correlated with the index variant rs10795433 in this study (r^2=0.54 and D'=1, based on HapMap r22 CEU data)

Supplementary Table 5: SNPs associated with MA among all individuals with a p-value of <1E-05.

SNPID	chr	position (hg18)	Allele 1	Allele 2	Fre-quency Allele1	Effect	SE	p-value	I^2 %	Sample Size	In Gene	Genes Within 100kb
rs11579312	1	30429159	t	c	0.69	0.11	0.025	9.7E-06	0	54116		
rs3795324	1	158909735	a	c	0.82	-0.15	0.031	9.4E-07	22	52716		CD48(dist=5425),SLAMF1(dist=26010),SLAMF7(dist=65736),CD84(dist=93805)
rs16827742	2	150615405	a	g	0.06	0.30	0.063	3.1E-06	12	35962		
rs9333289	2	187206352	t	c	0.71	-0.10	0.022	5.2E-06	0	54107	*ITGAV*	FAM171B(dist=60682)
rs9333290	2	187227583	t	g	0.29	0.11	0.023	5.0E-06	0	54107	*ITGAV*	FAM171B(dist=39451)
rs13006483	2	187230995	t	g	0.29	0.10	0.023	7.0E-06	0	54107	*ITGAV*	FAM171B(dist=36039)
rs12151442	2	187246092	t	c	0.70	-0.10	0.022	2.0E-06	0	54107	*ITGAV*	FAM171B(dist=20942)
rs13001028	2	187255140	a	g	0.70	-0.10	0.023	8.3E-06	0	54106		ITGAV(dist=1266),FAM171B(dist=11894)
rs13028817	2	187255744	t	g	0.70	-0.10	0.022	2.1E-06	0	54105		ITGAV(dist=1870),FAM171B(dist=11290)
rs12615659	2	187259552	a	t	0.30	0.11	0.022	1.3E-06	0	54105		ITGAV(dist=5678),FAM171B(dist=7482)
rs11678190	2	187268553	a	c	0.70	-0.10	0.023	5.1E-06	0	54107	*FAM171B*	ITGAV(dist=14679)
rs17750683	2	187328542	a	t	0.68	-0.11	0.022	1.4E-06	0	54105	*FAM171B*	ZSWIM2(dist=71910),ITGAV(dist=74668)
rs13026081	2	187334583	t	c	0.32	0.11	0.022	1.6E-06	0	54093	*FAM171B*	ZSWIM2(dist=65869),ITGAV(dist=80709)
rs1077216	3	46867165	t	c	0.07	0.20	0.044	5.2E-06	5	45096		MYL3(dist=7196),PRSS42(dist=16576),PTH1R(dist=27075),CCDC12(dist=71059)
rs13160548	5	38814607	t	c	0.69	-0.10	0.023	8.2E-06	14	53130	*OSMR-AS1*	LINC01265(dist=58475),OSMR(dist=67110)
rs12719264	5	119211839	a	g	0.30	-0.11	0.025	6.2E-06	29	54115		
rs2110904	6	107701464	t	c	0.65	0.10	0.022	8.9E-06	0	54116	*PDSS2*	
rs538641	8	103072879	a	g	0.05	0.28	0.062	7.8E-06	0	50048	*NCALD*	
rs1801239	10	16959058	t	c	0.90	-0.23	0.035	1.7E-10	18	54115	*CUBN*	RSU1(dist=59599)
rs17343073	10	16972202	a	t	0.90	-0.23	0.036	3.0E-10	0	54115	*CUBN*	RSU1(dist=72743)
rs6602163	10	17006772	a	g	0.83	-0.17	0.029	1.5E-09	5	54116	*CUBN*	
rs10795433	10	17009929	a	c	0.85	-0.20	0.031	1.3E-10	4	54116	*CUBN*	
rs12764441	10	72361657	t	c	0.48	-0.10	0.021	3.5E-06	0	54116		PCBD1(dist=43108),SGPL1(dist=50719)
rs3740393	10	104626645	c	g	0.21	0.13	0.028	6.1E-06	19	54048	*C10orf32-ASMT*	C10orf32(dist=11937),CYP17A1(dist=39365),CNNM2(dist=41420),WBP1L(dist=60634)
rs10899033	11	74070819	c	g	0.72	0.11	0.025	9.3E-06	0	54116		CHRDL2(dist=14303),MIR4696(dist=38142),POLD3(dist=39066),RNF169(dist=66742)
rs10498273	14	20214639	c	g	0.94	-0.21	0.047	9.6E-06	36	53131		ANG(dist=7537),RNASE4(dist=7573),OR6S1(dist=34949),EDDM3A(dist=69300),LOC254028(dist=69419),RNASE12(dist=85817),RNASE11(dist=86382),EDDM3B(dist=91787)
rs7145202	14	22161945	t	c	0.62	0.10	0.022	3.7E-06	0	54106		ABHD4(dist=10840),DAD1(dist=33962)
rs6572602	14	22163380	a	g	0.62	0.11	0.024	4.6E-06	0	41412		ABHD4(dist=12275),DAD1(dist=35397)
rs274173	19	61384255	c	g	0.17	-0.23	0.051	5.2E-06	12	38796	*GALP*	ZSCAN5B(dist=8615),ZNF444(dist=20181),ZSCAN5A(dist=40236),ZNF787(dist=59701)

rs6030216	20	40486448	t	c	0.17	0.12	0.027	6.0E-06	0	54115	*PTPRT*
rs4812598	20	40487956	c	g	0.83	-0.12	0.027	9.1E-06	0	54115	*PTPRT*
rs6513791	20	40491536	t	c	0.18	0.12	0.026	4.4E-06	12	54115	*PTPRT*
rs4810356	20	40491604	t	c	0.82	-0.13	0.028	7.6E-06	11	54115	*PTPRT*
rs6030232	20	40496297	a	t	0.82	-0.12	0.027	8.7E-06	0	54115	*PTPRT*
rs6030238	20	40498930	a	g	0.81	-0.12	0.026	6.0E-06	12	54115	*PTPRT*

Odds rations can be obtained by exponentiating the effect to the basis *e*.

Supplementary Table 6: SNPs associated with UACR among individuals without diabetes with a p-value of <1E-05.

SNPID	chr	position (hg18)	Allele 1	Allele 2	Fre-quency Allele1	Effect	SE	p-value	I^2%	Sample Size	In Gene	Genes Within 100kb
rs17377079	1	84999401	a	g	0.15	0.060	0.013	6.9E-06	9	46061		LPAR3(dist=52273),SSX2IP(dist=70573)
rs4072037	1	153428691	t	c	0.54	0.028	0.006	8.5E-06	0	46061	*MUC1*	MIR92B(dist=2901),THBS3(dist=3312),TRIM46(dist=4620),KRTCAP2(dist=16263),MTX1(dist=16423),GBAP1(dist=21549),GBA(dist=42172),DPM3(dist=49071),SLC50A1(dist=50733),EFNA1(dist=54681),FAM189B(dist=54929),SCAMP3(dist=63703),CLK2(dist=70592),HCN3(dist=85151),PKLR(dist=97017)
rs9333290	2	187227583	t	g	0.30	0.037	0.008	4.1E-06	3	46052	*ITGAV*	FAM171B(dist=39451)
rs13006483	2	187230995	t	g	0.30	0.035	0.008	6.7E-06	3	46052	*ITGAV*	FAM171B(dist=36039)
rs13001028	2	187255140	a	g	0.69	-0.034	0.008	9.9E-06	0	46052		ITGAV(dist=1266),FAM171B(dist=11894)
rs11678190	2	187268553	a	c	0.69	-0.035	0.008	8.7E-06	0	46052	*FAM171B*	ITGAV(dist=14679)
rs17750683	2	187328542	a	t	0.68	-0.035	0.008	4.6E-06	0	46052	*FAM171B*	ZSWIM2(dist=71910),ITGAV(dist=74668)
rs13026081	2	187334583	t	c	0.32	0.034	0.008	8.3E-06	0	46045	*FAM171B*	ZSWIM2(dist=65869),ITGAV(dist=80709)
rs4674086	2	201032130	t	c	0.46	0.028	0.006	8.7E-06	0	45053	*SPATS2L*	KCTD18(dist=29799),SGOL2(dist=66980)
rs9372871	6	127849645	t	c	0.89	-0.046	0.010	4.2E-06	2	45094	*SOGA3*	KIAA0408(dist=27417),C6orf58(dist=90367)
rs9372872	6	127849848	c	g	0.11	0.046	0.010	2.5E-06	0	46061	*SOGA3*	KIAA0408(dist=27620),C6orf58(dist=90164)
rs7739650	6	127850605	a	g	0.11	0.046	0.010	3.1E-06	2	46061	*SOGA3*	KIAA0408(dist=28377),C6orf58(dist=89407)
rs13220247	6	127850652	t	c	0.89	-0.046	0.010	3.4E-06	2	46061	*SOGA3*	KIAA0408(dist=28424),C6orf58(dist=89360)
rs9388580	6	127851073	t	c	0.89	-0.044	0.010	8.7E-06	6	46061	*SOGA3*	KIAA0408(dist=28845),C6orf58(dist=88939)
rs12668467	7	13598753	t	c	0.27	-0.043	0.009	4.1E-06	0	46061		
rs1801239	10	16959058	t	c	0.90	-0.054	0.012	4.4E-06	25	46061	*CUBN*	RSU1(dist=59599)
rs10795433	10	17009929	a	c	0.86	-0.045	0.010	8.7E-06	14	46061	*CUBN*	
rs2192224	15	24959369	t	g	0.13	0.048	0.011	6.1E-06	0	46061	*GABRG3*	LOC101928869(dist=26259)
rs7173577	15	53092295	a	g	0.45	-0.029	0.006	6.7E-06	0	46061		
rs1728867	15	53094106	a	g	0.45	-0.028	0.006	7.4E-06	0	46061		
rs951048	15	53094503	a	t	0.44	-0.028	0.006	7.8E-06	0	46061		
rs2414396	15	53094680	a	g	0.46	-0.029	0.006	4.1E-06	0	46061		
rs17818939	15	53096140	a	g	0.44	-0.028	0.006	9.9E-06	0	46061		
rs2899576	15	53107909	t	c	0.48	-0.029	0.006	5.7E-06	0	46035		
rs1528472	15	53108420	a	c	0.48	-0.030	0.007	3.1E-06	0	46056		
rs17238122	15	53109188	a	g	0.48	-0.030	0.007	4.8E-06	0	46054		
rs1528477	15	53111680	a	g	0.48	-0.030	0.007	6.6E-06	0	46061		
rs11858741	15	53112699	a	g	0.51	0.029	0.007	7.9E-06	0	46061		
rs4528660	18	3033516	t	c	0.91	-0.073	0.017	9.4E-06	3	33478		MYOM1(dist=23289),LPIN2(dist=31571),LOC727896 (dist=96895)

Supplementary Table 7: SNPs associated with UACR among individuals with diabetes with a p-value of <1E-05.

SNPID	chr	position (hg18)	Allele 1	Allele 2	Fre-quency Allele1	Effect	SE	p-value	I^2 %	Sample Size	In Gene	Genes Within 100kb [Closest Gene]
rs13427836	2	128744431	t	c	0.14	0.199	0.044	6.1E-06	10	5509	*HS6ST1*	UGGT1(dist=74712)
rs13428208	2	128744772	t	c	0.14	0.195	0.044	7.6E-06	10	5509	*HS6ST1*	UGGT1(dist=75053)
rs2405747	2	128748295	t	c	0.15	0.193	0.043	6.9E-06	14	5509	*HS6ST1*	UGGT1(dist=78576)
rs4662787	2	128752447	t	c	0.18	0.176	0.040	9.0E-06	0	5824	*HS6ST1*	UGGT1(dist=82728)
rs10183821	2	128753139	a	g	0.81	-0.169	0.038	9.3E-06	0	5825	*HS6ST1*	UGGT1(dist=83420)
rs13079877	3	2102845	a	g	0.45	0.148	0.033	5.6E-06	25	5825		CNTN4(dist=12705),CNTN4-AS2(dist=24248)
rs7634770	3	67012918	a	c	0.70	-0.142	0.030	2.7E-06	19	5825		[KBTBD8, dist=119174]
rs9876318	3	67014118	a	t	0.69	-0.144	0.030	2.0E-06	20	5824		[KBTBD8, dist=117974]
rs17738155	6	51264035	t	c	0.92	-0.241	0.053	5.9E-06	39	5825		[PKHD1, dist=324068]
rs947724	6	51274689	t	c	0.92	-0.239	0.053	7.5E-06	41	5825		[PKHD1, dist=313414]
rs7792461	7	29479920	t	g	0.39	0.130	0.029	5.1E-06	0	5825	*CHN2*	PRR15(dist=90032)
rs4722909	7	29481456	a	g	0.60	-0.134	0.029	3.2E-06	0	5823	*CHN2*	PRR15(dist=88496)
rs4722913	7	29482735	a	g	0.61	-0.131	0.029	4.2E-06	0	5825	*CHN2*	PRR15(dist=87217)
rs7798161	7	29483162	a	g	0.61	-0.130	0.029	4.7E-06	0	5825	*CHN2*	PRR15(dist=86790)
rs3828977	7	29486023	a	g	0.59	-0.131	0.029	4.9E-06	0	5825	*CHN2*	PRR15(dist=83929)
rs7922045	10	122991722	t	c	0.26	0.165	0.033	5.7E-07	0	5824		[FGFR2, dist=236111]
rs729014	10	122992796	t	c	0.15	0.202	0.043	2.4E-06	0	5825		[FGFR2, dist=235037]
rs649529	11	87647899	t	g	0.43	-0.147	0.033	9.3E-06	0	5825		CTSC(dist=18509),RAB38(dist=99616)

Supplementary Table 8: Discovery, replication and combined estimates for all index SNPs associated with UACR in diabetes in the discovery sample at p<1E-05

						discovery						replication						combined					
Marker	gene nearby	chr	position (hg18)	A 1	A 2	Freq A1	beta	SE	p-value	I^2 %	n	Freq A1	beta	SE	p-value	I^2 %	n	Freq A1	beta	SE	p-value	I^2 %	n
rs13427836	*HS6ST1*	2	128744431	t	c	0.14	0.20	0.04	6.1E-06	10	5509	0.15	0.16	0.07	3.13E-02	58	1890	0.15	0.19	0.04	6.31E-07	30	7399
rs13079877	*CNTN4*	3	2102845	a	g	0.45	0.15	0.03	5.6E-06	25	5825	0.50	0.04	0.05	5.16E-01	0	1880	0.46	0.12	0.03	2.40E-05	20	7705
rs9876318	*KBTBD8*	3	67014118	a	t	0.69	-0.14	0.03	2.0E-06	20	5824	0.69	0.08	0.06	1.56E-01	0	1897	0.69	-0.09	0.03	4.86E-04	37	7721
rs17738155	*PKHD1*	6	51264035	t	c	0.92	-0.24	0.05	5.9E-06	39	5825	0.92	0.06	0.10	5.30E-01	0	1896	0.92	-0.17	0.05	2.51E-04	42	7721
rs4722909	*CHN2*	7	29481456	a	g	0.60	-0.13	0.03	3.2E-06	0	5823	0.60	0.09	0.05	9.66E-02	40	1894	0.60	-0.08	0.03	9.92E-04	38	7717
rs7922045	*FGFR2*	10	122991722	t	c	0.26	0.17	0.03	5.7E-07	0	5824	0.23	-0.10	0.06	1.05E-01	35	1824	0.25	0.11	0.03	2.41E-04	39	7648
rs649529	*RAB38*	11	87647899	t	g	0.43	-0.15	0.03	9.3E-06	0	5825	0.43	-0.12	0.05	1.91E-02	0	1962	0.43	-0.14	0.03	5.84E-07	0	7787

A1 is the coded allele (effect allele), i.e. the beta corresponds to the effect by which UACR changes per each additional copy of the coded allele.
The I^2 statistic of the combined results was obtained from a separate analysis incorporating each discovery file with single GC-correction and the replication files. Standard error (SE) and p-value of the combined results are based on double-GC corrected results as described in the methods.

Supplementary Table 9: Association results for the index SNPs near *RAB38/CTSC* and in *HS6ST1* in the DCCT/EDIC Study

incident microalbuminuria (1244 individuals [268 cases]; primary endpoint)					
SNP	effect alelle	frequency of effect allele	effect	se	p-value
rs649529	T	0.42	0.04	0.09	0.64
rs13427836	T	0.14	-0.18	0.14	0.20
time to macroalbuminuria or ESRD (1304 individuals [133 cases]; secondary endpoint)					
SNP	effect alelle	frequency of effect allele	effect	se	p-value
rs649529	T	0.42	0.24	0.14	0.09
rs13427836	T	0.14	-0.31	0.22	0.16

Cox proportional hazards regression models were used to estimate hazard ratios after adjustment for cohort status (primary vs. secondary), treatment (intensive vs. conventional), cohort*treatment interaction (stratified by DCCT year of entry), age of diagnosis squared, sex, diabetes duration squared, body mass index, blood pressure, triglyceride, HDL-C, total cholesterol, smoking (all at baseline), as well as time-dependent updated mean A1C, and time-dependent indicators for hypertension diagnosis and treatment. Imputation quality (rs13427836) and call rate (rs649529) were both >=0.99.